

UNIVERSITY OF ALBERTA

**Synthesis of D-Myo-Inositol-1,4,5-
tris(dihydrogenphosphate) and Synthetic Studies
on the Farnesyl Transferase Inhibitors CP-
225,917 and CP-263,114**

by

Xiao He



A thesis submitted to the Faculty of Graduate Studies and
Research in partial fulfillment of the requirements for the
degree of Doctor of Philosophy.

DEPARTMENT OF CHEMISTRY

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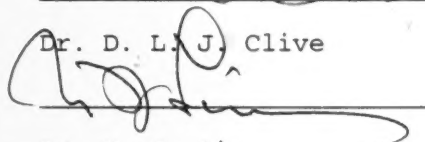
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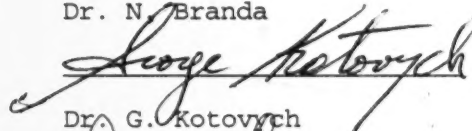
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ABSTRACT

D-Glucose had previously been converted in this laboratory into the propargyl silane aldehyde **28** which, on treatment with camphorsulfonic acid, cyclized with retention of silicon. We repeated this procedure and assigned the stereochemistry to the allenic product **29**. This material was then elaborated via ketone **88** into **20**, which was a known precursor of D-myoinositol-1,4,5-tris(dihydrogenphosphate). Selective reduction of the advanced intermediate **88** was accomplished with $\text{Bu}_2\text{SnCl}_2/\text{Bu}_2\text{SnH}_2$, a reagent mixture that shows a very strong preference for generating equatorial alcohols.

The cyclization step leading to allene **29** was studied by examining a number of model compounds; the unusual retention of silicon appears to be limited to highly oxygenated substrates, such as **28** and its all benzyl analog **37**. Although the mechanistic details are unclear, the cyclization of ω -formyl propargyl silanes represents a route to carbocycles that incorporate an allene appendage; in favorable cases the yield is good and the reaction can be highly stereoselective.

In the second part of this thesis, the oxy-Cope rearrangement was studied as a key step of our approach to synthesis of CP-225,917 and CP-263,114. Anionic rearrangement [e.g., **85** $\rightarrow$ **87** (compound numbering of part 2)] does not proceed if the ethylidene unit (see compound **26**,

part 2) is modified by an increase in chain length or in the number of substituents. However, in refluxing *N*-methylpyrrolidinone (NMP), siloxy-Cope rearrangement, e.g. **83** → **87**, does take place and gives the desired products in good yield (after correction for recovered starting material). These results are now being used to reach more advanced compounds.

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LIST OF ABBREVIATIONS

Ac.....	acetyl
Bn.....	benzyl
BOM.....	benzyloxymethyl
t-Bu.....	tert-butyl
Bz.....	benzoyl
CSA.....	camphorsulfonic acid
cf.	compare
DABCO.....	1,4-diazabicyclo[2.2.2]octane
DBU.....	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC.....	<i>N,N</i> -dicyclohexylcarbodiimide
DDQ.....	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD.....	diethyl azodicarboxylate
DIBAL.....	diisobutylaluminum hydride
DMAP.....	4-(dimethylamino)pyridine
DMF.....	dimethylformamide
DMSO.....	dimethyl sulfoxide
FPTase.....	farnesyl protein transferase
FTIs.....	farnesyl protein transferase inhibitors
GDP.....	guanosine diphosphate
GTP.....	guanosine triphosphate
HMPA.....	hexamethylphosphoric triamide
KHMDS.....	potassium hexamethyldisilazane
LDA.....	lithium diisopropylamide
LHMDS.....	lithium hexamethyldisilazane

MAD.....methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide)
MCPBA.....*m*-chloroperoxybenzoic acid
MOM.....methoxymethyl
NMO.....4-methylmorpholine *N*-oxide
NMP.....1-methyl-2-pyrrolidinone
PCC.....pyridinium chlorochromate
PDC.....pyridinium dichromate
Ph.....phenyl
Pmb.....*p*-methoxybenzyl
PPTs.....pyridinium *p*-toluenesulfonate
Pr.....propyl
Py.....pyridine
SEM.....2-(trimethylsilyl)ethoxymethyl
TBAF.....tetrabutylammonium fluoride
TBDPS.....*tert*-butyldiphenylsilyl
TBS.....*tert*-butyldimethylsilyl
TES.....triethylsilyl
TMS.....trimethylsilyl
Tf.....trifluoromethanesulfonyl
TFA.....trifluoroacetic acid
TFAA.....trifluoroacetic anhydride
THF.....tetrahydrofuran
THP.....tetrahydropyran
TPAP.....tetra-*n*-propylammonium perruthenate
Tr.....triphenylmethyl
Ts.....*p*-toluenesulfonyl

Part 1

Synthesis of D-Myo-Inositol-1,4,5-tris(dihydrogenphosphate) and Related Study on the Cyclization by an Unusual Ene Reaction

Introduction

Inositol phosphates play essential roles in the coupling of cell surface receptors to cellular responses, and the chemistry and biochemistry of these compounds have been reviewed extensively.¹ D-*myo*-inositol-1,4,5-tris(dihydrogenphosphate), Ins(1,4,5)P₃, (**1**) is a very important messenger in the metabolism of calcium, and consequently, it has been the object of a great deal of

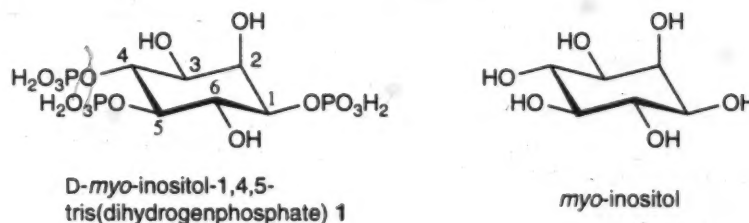


Figure 1 structure of **1** and *myo*-inositol

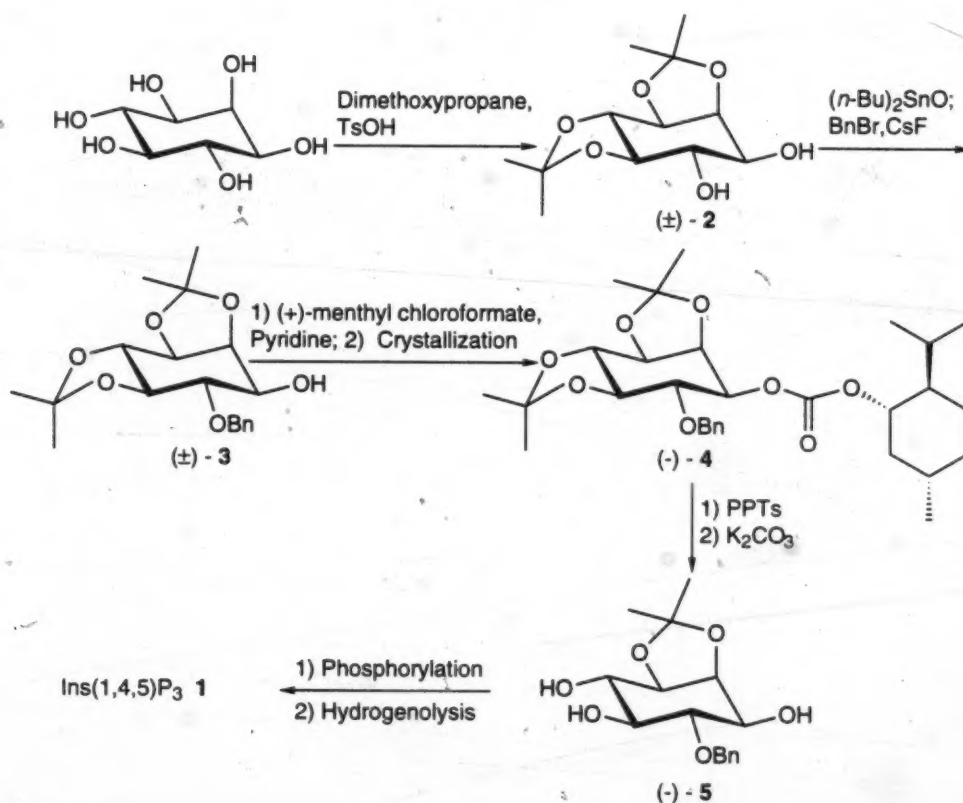
synthetic work.^{1,2} The compound is difficult to isolate, and is extremely expensive (ca. \$400-1000 per mg, depending on source), and is needed for biochemical studies of calcium metabolism.

Many of the published synthetic approaches to Ins(1,4,5)P₃ (**1**) begin with myo-inositol. A resolution is usually employed in the synthesis of optically pure Ins(1,4,5)P₃ (**1**).^{1,3,4} Most optical resolutions in the synthesis of inositol phosphates rely on the conversion of racemic inositol derivatives into a pair of diastereomers, which are then separated by crystallization or chromatography.

1. Chemical resolution method

A recent example of chemical resolution was reported by

Scheme 1

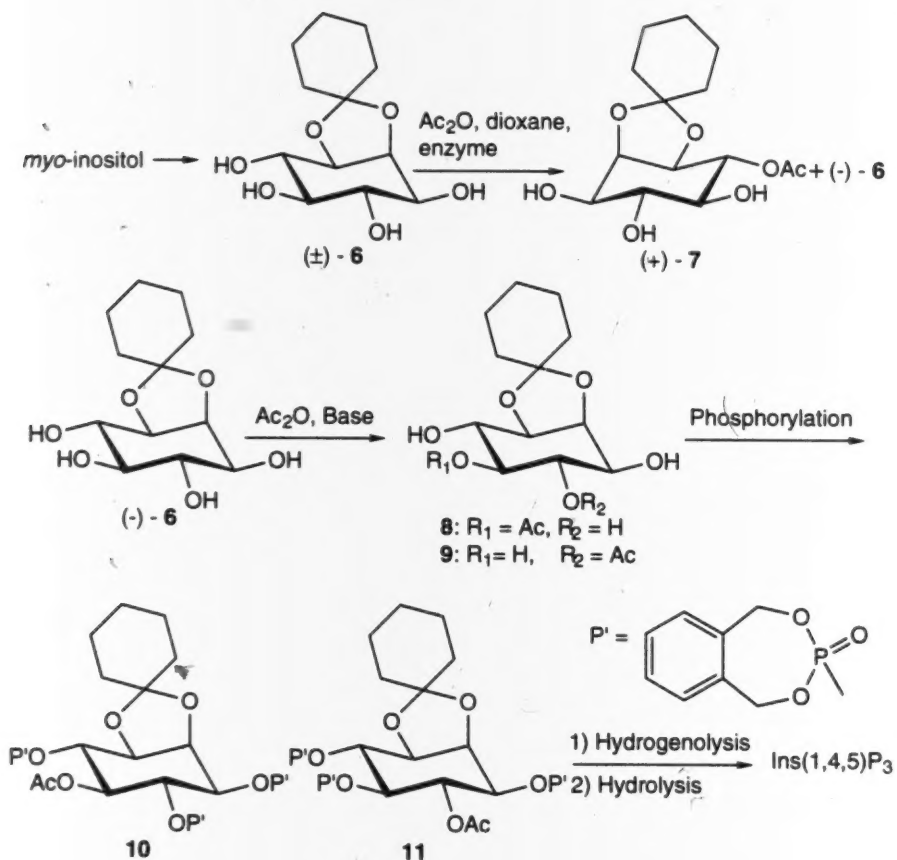


Bittman's group.³ Myo-inositol was converted into ($\pm$)-2,3:4,5-di-*O*-isopropylidene-myoinositol [($\pm$)-2] (Scheme 1). Regioselective benzylation of the 6-hydroxyl group gave ($\pm$)-6-benzyl-2,3:4,5-di-*O*-isopropylidene-myoinositol [($\pm$)-3]. Reaction of ($\pm$)-3 with (+)-menthyl chloroformate gave, after crystallization, the corresponding diastereomer (-)-4, from which (-)-5 was easily obtained. Conversely, reaction of ($\pm$)-3 with (-)-menthyl chloroformate, followed by crystallization and alkaline hydrolysis, resulted in (+)-5. After phosphorylation and hydrogenolysis Ins(1,4,5)P₃ (1) was obtained from (-)-5.

2. Enzymatic resolution method

By using enzymatic esterification in an organic solvent (see Scheme 2),⁴ racemic 2,3-mono-*O*-cyclohexylidene-myoinositol ($\pm$)-6, which was prepared from myoinositol, was efficiently resolved. Starting from optically pure (-)-6, a mixture of 6- and 5- acetylated products 8 and 9 was obtained by acetylation. The mixture was subjected to phosphorylation to give the corresponding products 10 and 11, which were separated by chromatography. Removal of the *O*-xylylene group in 11 was accomplished by hydrogenolysis. At the same time the cyclohexylidene group was hydrolyzed by the phosphoric acid liberated during the hydrogenolysis. Further deprotection of 11, with concentrated ammonia solution, resulted in Ins(1,4,5)P₃.

Scheme 2

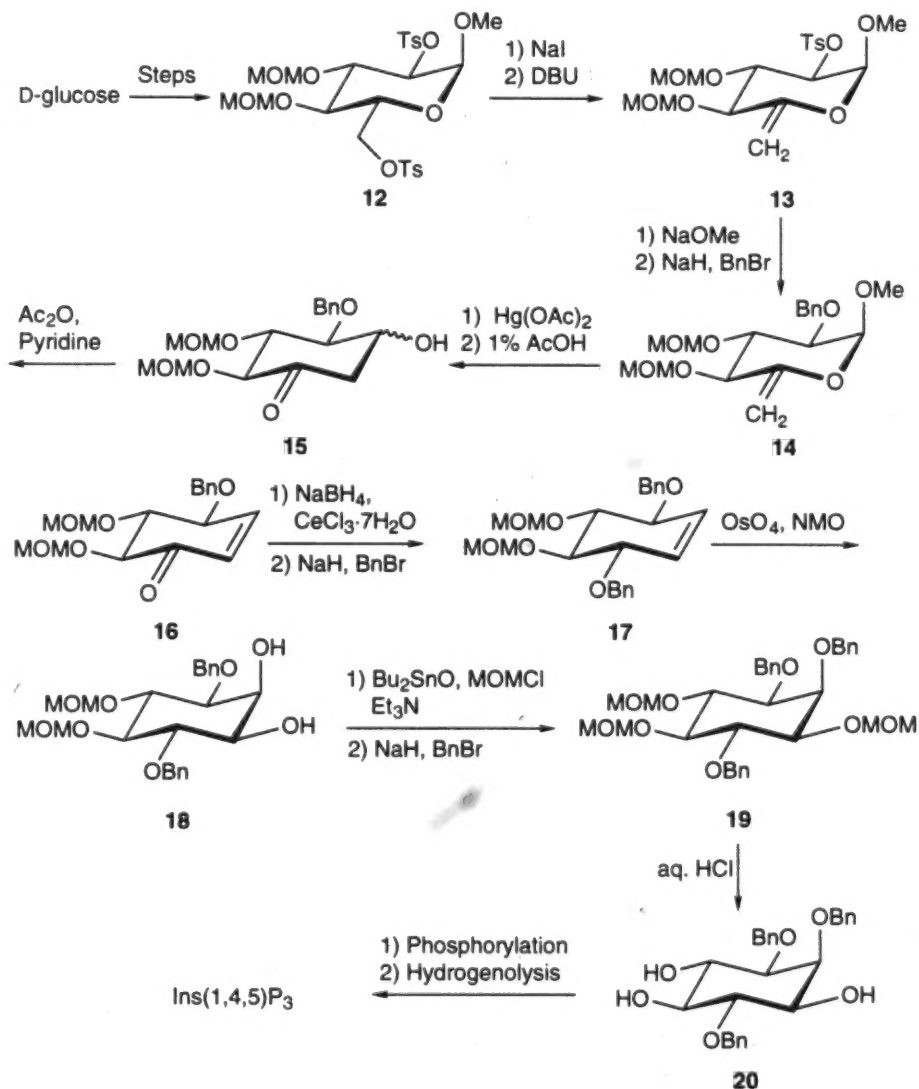


Obviously, optical resolution can be avoided by using optically pure starting materials. There are a few methods by which Ins(1,4,5)P₃ (**1**) has been obtained from compounds in the chiral pool such as $(-)$ -quinic acid⁵ and D-pinnitol.⁶ Recently D-glucose^{7,8} has been used for this propose. In the case of D-glucose, the pyranose ring was converted into the required carbocycle by Ferrier⁹ rearrangement and, in this laboratory, an unusual ene reaction was used (see below).¹⁰

3. Sato's D-glucose approach⁷

Starting from D-glucose, the differentially protected tosyl glycoside **12** was synthesized. Treatment of **12** with NaI

Scheme 3



and then DBU gave the 6-deoxyhex-5-enopyranoside derivative **13** (Scheme 3). Detosylation of **13**, followed by protection

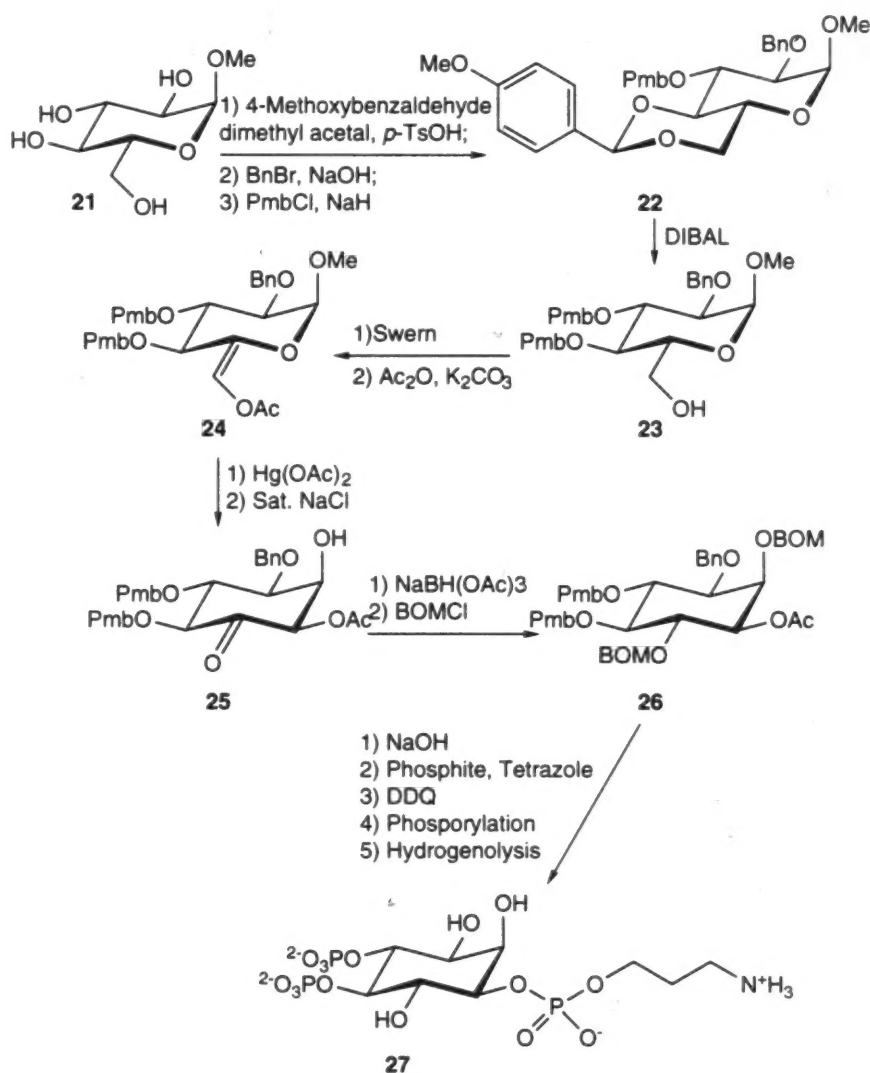
with a benzyl group, resulted in **14**. Ferrier reaction of **14** afforded partially protected tetrahydroxycyclohexanone derivative **15**. Dehydration of **15** gave enone **16**, which was reduced and protected by benzylation. The resulting product **17**, which has C₂ symmetry, was treated with OsO₄, and gave the *myo*-inositol derivative **18**. Regioselective protection of the vicinal hydroxyls, followed by benzylation of the remaining hydroxyl, furnished the fully protected compound **19**. Hydrolytic removal of the methoxymethyl groups of **19** then gave 2,3,6-tri-*O*-benzyl-D-*myo*-inositol (**20**), which had previously been converted into Ins(1,4,5)P₃ (**1**).

4. Prestwich's D-glucose approach⁸

A tethered version of (**1**) has been made from D-glucose by Prestwich and his group. A Ferrier rearrangement was also used to establish the D-*myo*-inositol skeleton, and the synthetic route is summarized in Scheme 4. Selective protection of the C(4) and C(6) hydroxyls of methyl α -D-glucoside **21**, followed by monobenzylation, and *p*-methoxybenzylation of the remaining hydroxyl, gave the fully protected ether **22**. Regioselective ring opening of the *p*-methoxybenzylidene acetal then gave compound **23**. Swern oxidation of the alcohol gave the corresponding aldehyde, which was converted directly into the enol acetate **24**. Ferrier rearrangement of **24** resulted in the desired ketone **25**, which was stereoselectively reduced and then protected at C(2) and C(6) as the bis-benzyloxymethyl (BOM) ether **26**.

Selective cleavage of the acetyl group enabled introduction of a aminoalkyl modified phosphate group and, following removal of the Pmb groups, phosphorylation, and release of the remaining hydroxyls, **27**, was obtained. This substance is a tethered derivative of **1**.

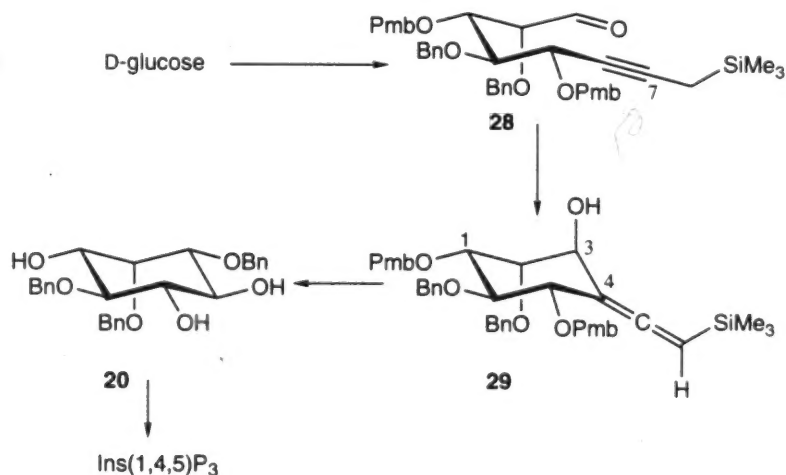
Scheme 4



5. Clive's D-glucose approach¹⁰

Clive's synthesis, whose concluding steps are part of the research section of this thesis, is based on a type of ene¹¹ reaction for converting a linear chain into a carbocycle (Scheme 5). The synthetic plan was to convert D-glucose into silicon-substituted acetylenic aldehyde **28**, where the silicon moiety was chosen so as to facilitate an ene reaction that affords **29**. The latter molecule seemed properly constituted

Scheme 5

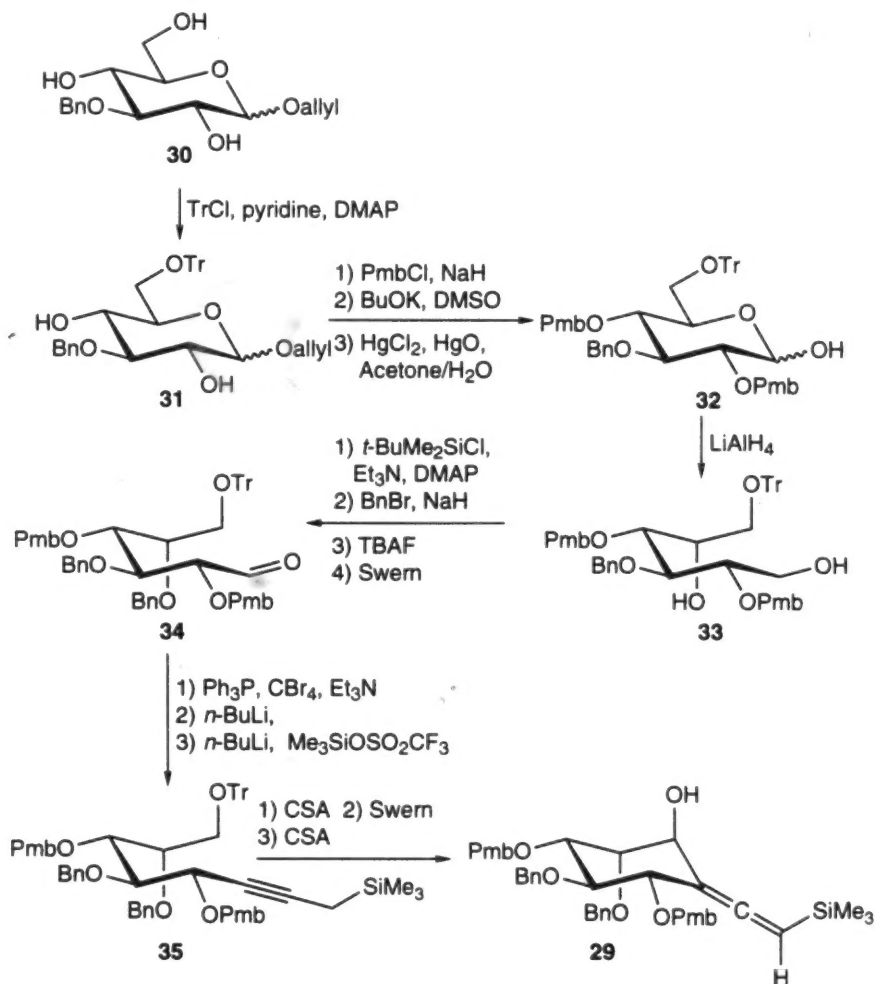


for elaboration into **20**, which had been converted¹² by others into D-*myo*-inositol-1,4,5-tris(dihydrogenphosphate).

Aldehyde **29** was prepared as summarized in Scheme 6. D-glucose was converted in three steps¹³ (76% overall) into the allyl glucopyranosides **30**. The C(6) primary hydroxyl was protected by tritylation (**30** → **31**), and the remaining two hydroxyls by conversion into their *p*-methoxybenzyl ethers. Deallylation was effected by the two-step method of double

bond isomerization,¹⁴ followed by hydrolysis¹⁵ of the resulting enol ethers. The resulting lactols **32** were reduced to glucitol **33**, and the primary hydroxyl was silylated. Benzylation of remaining secondary hydroxyl and removal of the silicon group, followed by Swern oxidation, gave aldehyde

Scheme 6



34. Construction of the acetylene unit was initiated by sequential treatment with $\text{CBr}_4/\text{Ph}_3\text{P}/\text{Et}_3\text{N}$ and $n\text{-BuLi}$.¹⁶

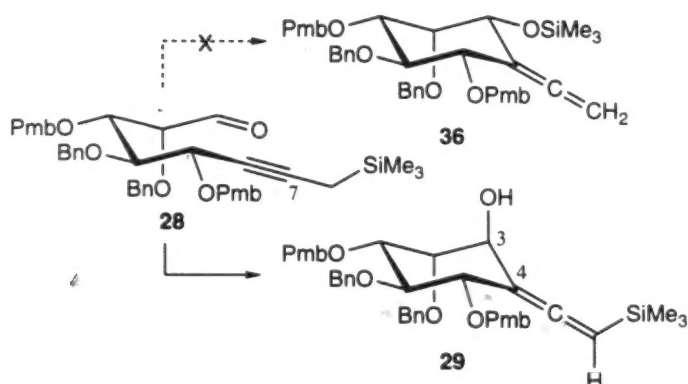
Deprotonation with *n*-BuLi, and reaction with Me₃SiCH₂OSO₂CF₃ gave propargyl silane **35**. Finally, detritylation of **35** was accomplished with no loss of the silicon group, and then Swern oxidation gave the key aldehyde **28** (see Scheme 5) needed for ene cyclization.

Ene cyclization was effected in the presence of camphorsulfonic acid, and **28** was transformed stereoselectively into **29**.¹⁷ The conditions for this ring closure with retention of silicon were optimized, it being found that use of camphorsulfonic acid (CSA) in PhMe gave **29** in 91% yield.¹⁸ Conversion of **29** into **20** required a number of apparently simple operations: stereochemical inversion at C(3), benzylation of the resulting alcohol, oxidative cleavage of the exocyclic double bond at C(4), and reduction of the resulting carbonyl to an equatorial alcohol. These operations proved unexpectedly troublesome. However, each was eventually achieved in good yield - but only after considerable effort to establish the proper choice and sequence of reagents (See Results and Discussion).

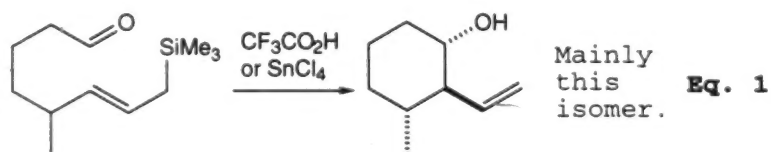
6. Cyclization with propargyl silane

In the early work of Clive's approach,¹⁷ it was expected that the ene pathway of the propargyl silane **28** (Scheme 7) would be in the sense **28** → **36**¹⁹ (with subsequent hydrolysis of the silyl ether), or with direct loss²⁰ of the silicon unit. This expectation was based on the fact that allyl

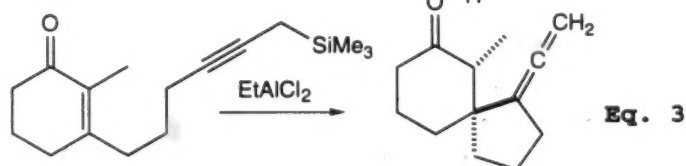
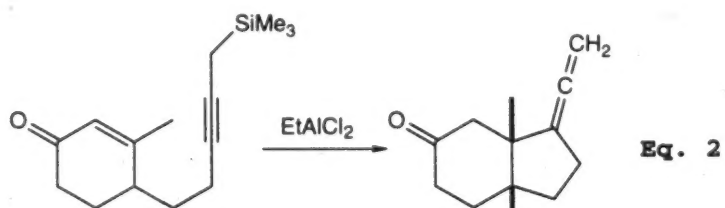
Scheme 7



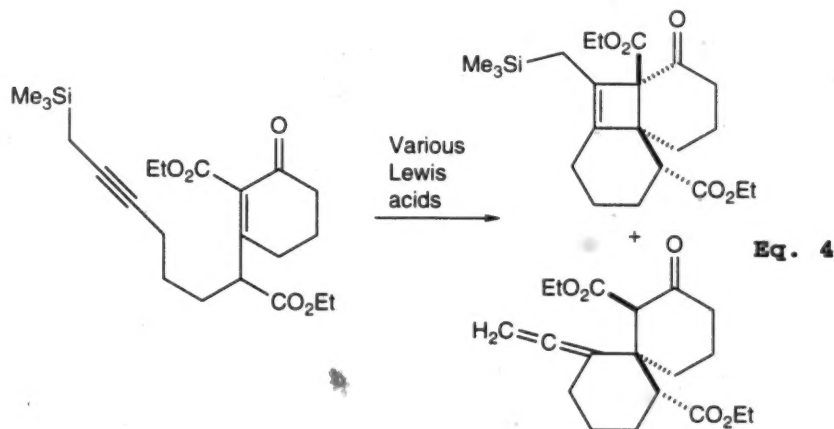
silanes are known²³ to undergo cyclization²⁴ (see eq 1^{23a}) formally related to the desired process. In the event, the silicon unit did not migrate, nor was it lost; as described earlier, only **29** was formed.



Several cases have been reported in which α,β -unsaturated ketones incorporating a suitably located propargyl silane unit undergo cyclization to afford allenes

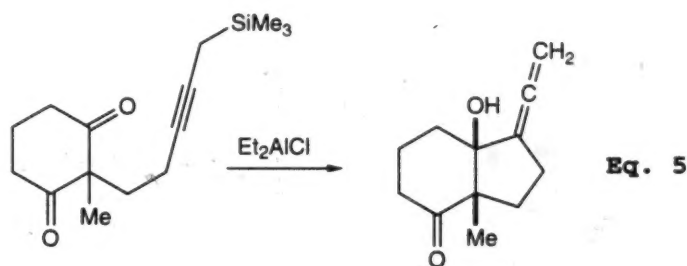


that contain a spiro- or linearly-fused bicyclic structure, as illustrated in eq 2^{21a} and 3.^{21a} The silicon group is



lost²⁵ during the cyclization, except in one case (eq 4),²⁶ where the expected product was accompanied by a substance arising formally by [2+2] cycloaddition.

Reactions such as those given in equations 2 and 3, and related processes,²⁷ have been examined in some detail,²¹ and used in natural product synthesis.²⁸ However, related cyclizations directly onto a carbonyl group have received little attention, and we know of only one prior example (see eq 5).²²



Results and discussion

1. Observations on the Closure of Propargyl Silanes onto Aldehyde Groups

In view of the unexpected retention of silicon in the inositol work described above, we investigated the closure of propargyl silanes onto aldehyde carbonyls, and have also examined corresponding cyclizations with ketones and acetals.²⁹ The reaction is a general route to five- and six-membered carbocycles, but only in certain situations is the silicon group retained.³⁰

The starting materials **37-44** (see Figure 2) were

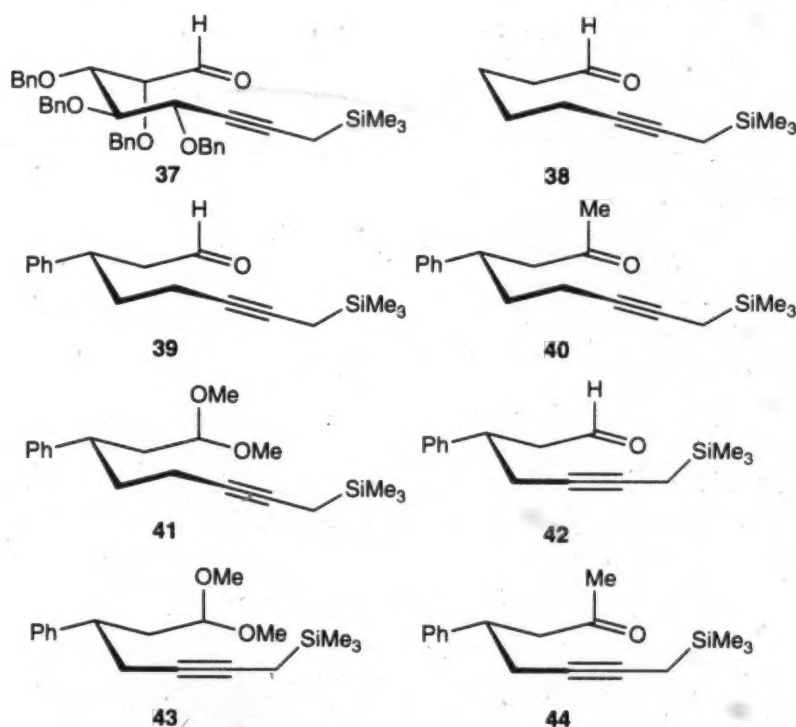
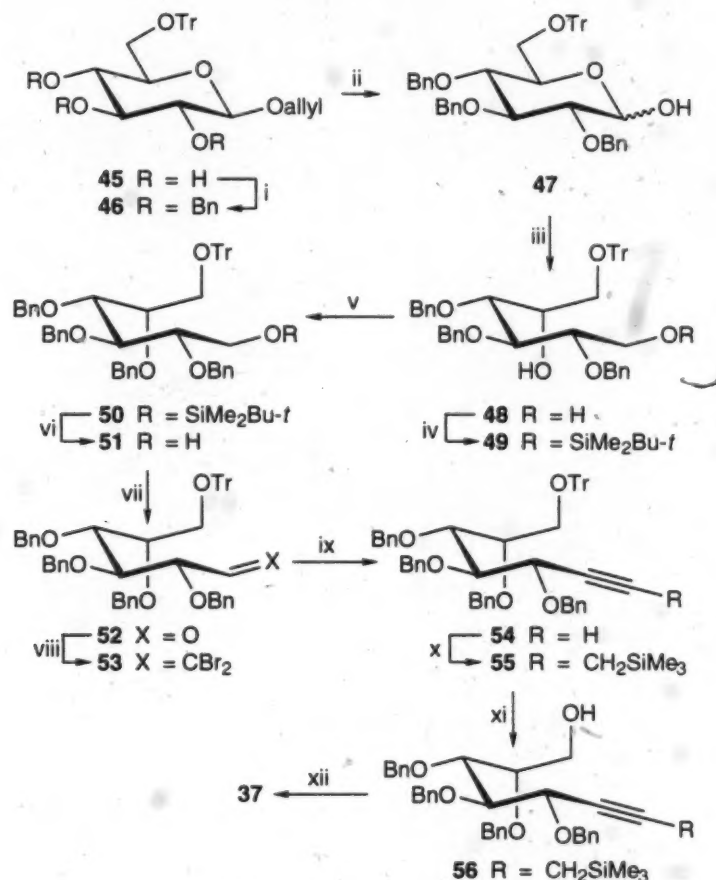


Figure 2 Structure of **37-44**

prepared by standard reactions, which are presented in the following paragraphs.

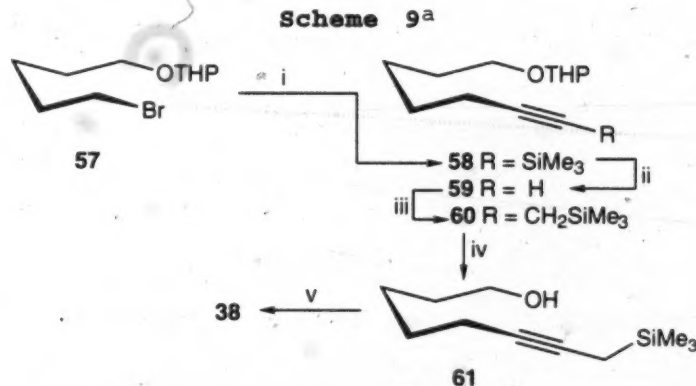
Scheme 8^a



^aKey: (i) NaOH, BnCl, 120 °C, 36 h, 87%; (ii) DMSO, *t*-BuOK, 100 °C, 1 h; HgO, HgCl₂, acetone-water, 4 h, 88%; (iii) LiAlH₄, THF, 0 °C to room temperature, 4 h, 95%; (iv) *t*-BuMe₂SiCl, Et₃N, DMAP, CH₂Cl₂, room temperature, 16 h, 95%; (v) NaH, THF, BnBr, reflux, 14 h, 94%; (vi) TBAF, THF, room temperature, 4 h, 97%; (vii) DMSO, (COCl)₂, Et₃N, 89%; (viii) Ph₃P, CBr₄, CH₂Cl₂, -20 °C, then cool to -60 °C and add Et₃N, then warm to room temperature, 30 min, 76%; (ix) *n*-BuLi, THF, -78 °C, 2 h, 78%; (x) *n*-BuLi, Me₃SiCH₂OSO₂CF₃, HMPA, THF, -78 °C to room temperature, 10 h, 78%; (xi) CSA, MeOH, room temperature, 24 h, 94%; (xii) DMSO, (COCl)₂, Et₃N, 84%.

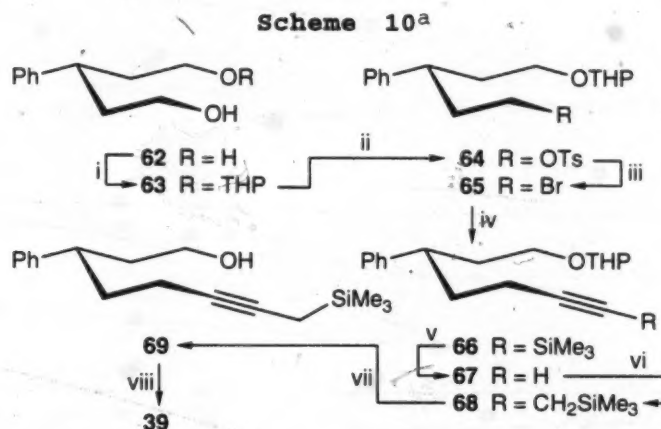
Aldehyde **37** was prepared as summarized in Scheme 8. Starting from 2-propenyl- β -D-glucopyranoside **45**,³¹ three hydroxyls were protected by benzylation. Deallylation gave lactols **47**, which were reduced to the glucitol **48**. Selective silylation of the primary hydroxyl, benzylation of remaining secondary hydroxyl, followed by removal of the silicon group and Swern oxidation resulted in aldehyde **52**. Construction of the acetylene unit, as described before (See: **34** $\rightarrow$ **35**), gave propargyl silane **55**. Detritylation of **55** was easily accomplished, and Swern oxidation then gave aldehyde **37** for the ene cyclization experiments.

The preparation of **38** is shown in Scheme 9. Homologation of compound **57**³² (**57** $\rightarrow$ **58**), followed by desilylation, gave terminal alkyne **59**.³³ After the



^aKey: (i) $\text{Me}_3\text{SiC}\equiv\text{CH}$, $n\text{-BuLi}$, THF, HMPA, -78°C , then room temperature, 15 h, 94% after correction for recovered **57** (35%); (ii) K_2CO_3 , MeOH, 0°C , 5 h, then room temperature, 12 h, 94%; (iii) $n\text{-BuLi}$, THF, -78°C , $\text{Me}_3\text{SiCH}_2\text{OSO}_2\text{CF}_3$, HMPA, room temperature, 18 h, 91% after correction for recovered **59** (18%); (iv) $\text{TsOH}\cdot\text{H}_2\text{O}$, MeOH-water, reflux, 3 h, 93%; (v) DMSO, $(\text{COCl})_2$, Et_3N , 80%.

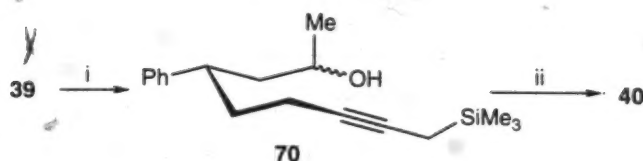
propargylsilane moiety had been built up, by the method used previously, deprotection of the THP ether and Swern oxidation gave **38**.



^aKey: (i) Dihydropyran, TsOH.H₂O, room temperature, 24 h, 66% after correction for recovered **62** (36%); (ii) TsCl, pyridine, DMAP, CH₂Cl₂, room temperature, 12 h, 63%; (iii) LiBr, acetone, reflux, 2 h, 95%; (iv) Me₃SiC≡CH, *n*-BuLi, THF, HMPA, -78 °C, then room temperature, 12 h, 81%; (v) K₂CO₃, MeOH-THF, 0 °C, 6 h, then room temperature, 12 h, 94%; (vi) *n*-BuLi, THF, -78 °C, Me₃SiCH₂OSO₂CF₃, HMPA, room temperature, 10 h, 92%; (vii) TsOH.H₂O, MeOH-water, reflux, 4 h, 89%; (viii) Swern, 90%.

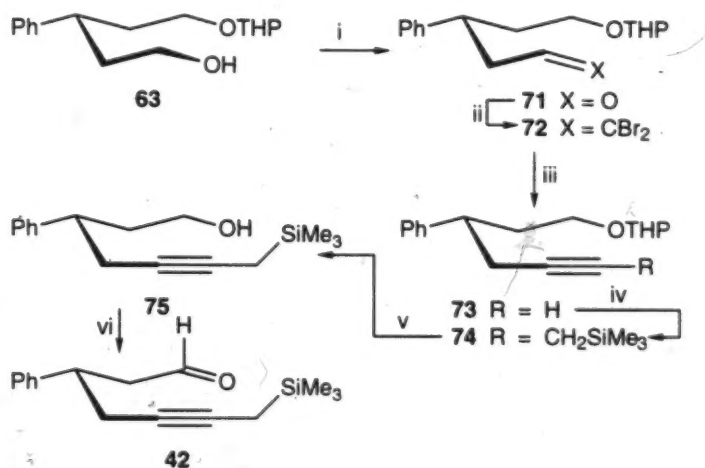
Compound **39** was prepared, as summarized in Scheme 10. The starting material was the 1,5-diol **62**.³⁴ Monoprotection of **62**, followed by tosylation of the remaining hydroxyl, gave tosylate **64**. Conversion of **64** into the bromide, followed by five standard steps, described earlier, gave **39**.

Ketone **40** was obtained as shown in Scheme 11. Starting from **39**, Grignard reaction followed by oxidation of the resulting alcohol gave compound **40**.

Scheme 11^a

^aKey: (i) MeMgBr, Et₂O, 0 °C to room temperature, 2 h, 90%;
(ii) PCC, 3Å sieves, CH₂Cl₂, 25 min, 90%.

The synthesis of aldehyde 42 started from monoprotected diol 63. After oxidation of 63, the corresponding aldehyde 71 was subjected to the standard series of reactions, described earlier, to afford compound 42, as shown in Scheme 12.

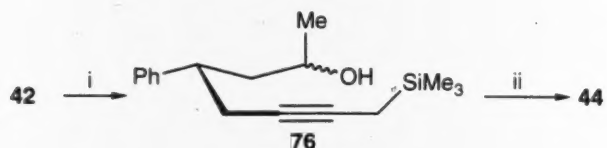
Scheme 12^a

^aKey: (i) PCC, 3Å sieves, CH₂Cl₂, 35 min, 82%; (ii) Ph₃P, CBr₄, CH₂Cl₂, -20 °C, then cool to -60 °C and add Et₃N, then warm to room temperature, 30 min, 76%; (iii) *n*-BuLi, THF, -78 °C, 2 h, then room temperature, 30 min, 94%; (iv) *n*-BuLi, THF, -78 °C, Me₃SiCH₂OSO₂CF₃, HMPA, room temperature, 10 h, 86%; (v) TsOH·H₂O, MeOH-water, reflux, 3.5 h, 98%; (vi) PCC, 3Å sieves, CH₂Cl₂, 30 min, 90%.

Ketals **41** and **43** were made by ketalization of **39** and **42** with $\text{YbCl}_3 \cdot 6\text{H}_2\text{O}$ and $\text{CH}(\text{OMe})_3$ in MeOH , respectively.

Ketone **44** was prepared as shown in Scheme 13.

Scheme 13^a



^aKey: (i) MeMgBr , Et_2O , 0°C , 2 h, 90%; (ii) PCC , $3\text{\AA}$ sieves, CH_2Cl_2 , 30 min, 92%.

In studying the ene reaction, we tried Lewis acids, as well as $\text{CF}_3\text{CO}_2\text{H}$, CSA , and TBAF . With the highly oxygenated substance **37** (Table 1, entry 1) and ketals **41** and **43** (Table 1, entries 6 and 8) the silicon unit is retained. The structure of **37a** was established by X-ray analysis, and the similarity of the ^1H NMR signal for the vinyl hydrogen with the corresponding signal for **29** suggested that **37a** and **29** have the same stereochemistry. The fact that the hydroxyl in **29** is axial was subsequently confirmed by conversion of **29** into **20** (see following part of Results and Discussion). The preferred conformation of **38a** is tentatively assigned as shown, based on the observation of a coupling constant of >3 Hz for coupling³⁵ between the $\text{CH}(\text{OH})$ proton and the allene CH_2 . An equatorial hydrogen would be associated with J of 1.2 Hz.³⁵ The stereochemical assignments to **39a** and **39b** were made on the basis of ^1H NMR measurements: Compound **39a** has signals centered at δ 3.14 [$\text{C}(5)\text{H}$] and 4.57 [$\text{C}(1)\text{H}$], while

the corresponding values for **39b** are δ 2.71 [C(5)H] and 4.15 [C(1)H]. The signal at δ 4.15 has larger J values than that at 4.57, as expected for an axial hydrogen. The acetate derived from **39a** has only small couplings (2.8 Hz) for the C(1)H signal, corresponding to an equatorial hydrogen [CH(OAc)]. The tentative stereochemical assignments to **40a** and **40b** were made on the basis that the signal for C(5)H in **40a** is at lower field than in **40b** (δ 3.14 versus 2.78). Similar arguments were used in the case of **41b** and **41c** to

Table 1.^a Cyclization with propargyl silanes

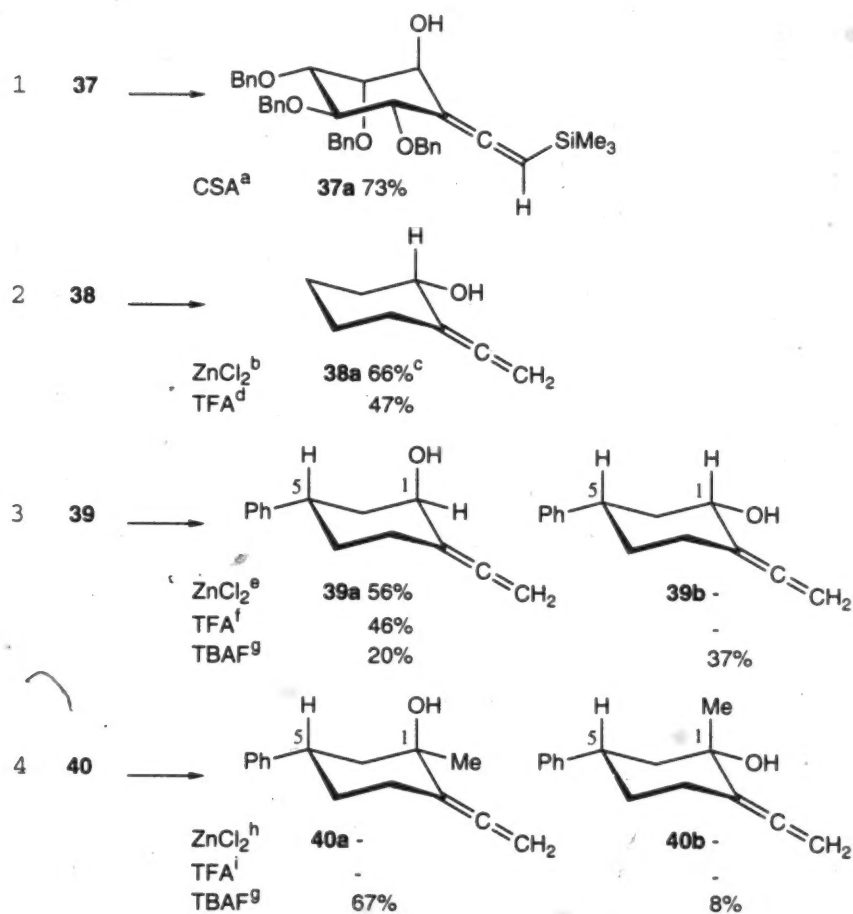
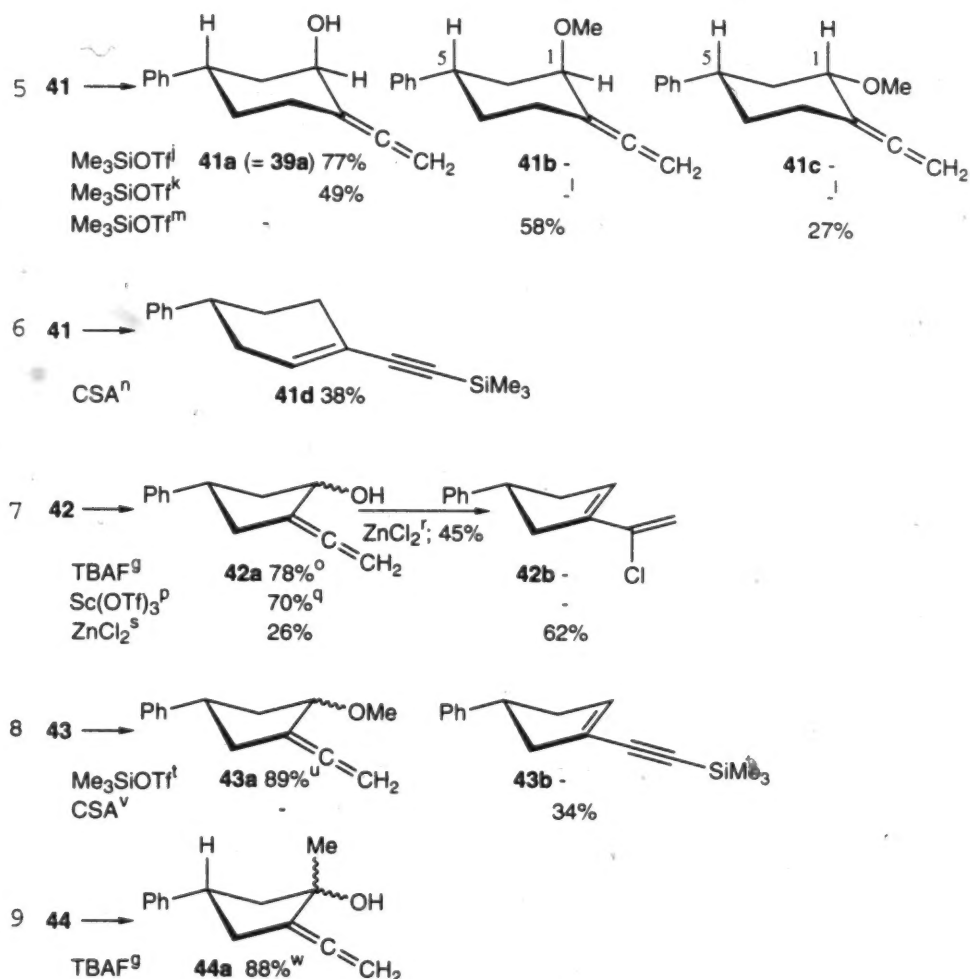


Table 1 (continued)



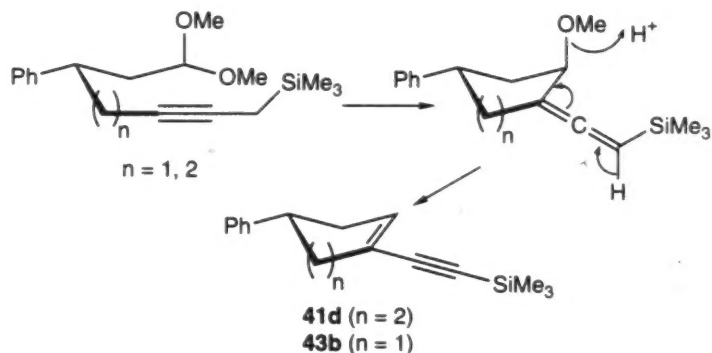
^aCSA, PhMe, room temperature, 5 h; ^bZnCl₂, CH₂Cl₂, 0 °C, 2.5 h; ^cPreferred conformation of **38a** is a tentative assignment. We do not imply that the compound is generated in this conformation; ^dTFA, CH₂Cl₂, -78 °C, 30 min; ^eZnCl₂, CH₂Cl₂, 0 °C, 3 h; ^fTFA, CH₂Cl₂, -78 °C, 1 h; ^gTBAF, THF, 0 °C, 1 h; ^hZnCl₂, CH₂Cl₂, 0 °C, 20 h; no reaction; ⁱTFA, CH₂Cl₂, 0 °C, 12 h; no reaction; ^jMe₃SiOSO₂CF₃ (catalytic), CH₂Cl₂, -78 °C to room temperature, 11 h; ^kMe₃SiOSO₂CF₃ (catalytic), CH₂Cl₂, -78 °C, 3 h, yield corrected for recovered starting material; ^lA 1.2:1.0:1.3 mixture of **41** (corresponding to 13% recovery), **41b** (corresponding to 12% yield), and **41c** (corresponding to 16% yield); ^mMe₃SiOSO₂CF₃ (1 equiv), CH₂Cl₂, -78 °C, 3 h; ⁿCSA, CH₂Cl₂, room temperature, 48 h; ^oEpimer mixture (55:45);

PSc(OSO₂CF₃)₃, MeNO₂, room temperature, 12 h; ^qEpimer mixture (1:1); ^rZnCl₂, CH₂Cl₂, room temperature, 24 h; ^sZnCl₂, CH₂Cl₂, 0 °C to room temperature, 14 h; ^tMe₃SiOSO₂CF₃ (1 equiv), CH₂Cl₂, -78 °C, 1.5 h; ^uEpimer mixture (3:2); ^vCSA, CH₂Cl₂, room temperature, 20 h; ^wEpimer mixture (1:7.2).

make the tentative assignments shown.³⁶ The epimers of **42a** and **43a** were not separated, and no stereochemical assignments were made for these compounds or for **44a**, which was also obtained as a chromatographically inseparable mixture.

We interpret the formation of **41d** and **43b** according to the process of Scheme 14, where the stereochemistry shown for the intermediate allenic silanes is arbitrary.

Scheme 14



The silicon unit is needed for the cyclization to occur.^{17,30} Possibly, the transition state has a partial positive charge on C(7) (see structure **28** in Scheme 5, page 8, and Scheme 7, page 11 for numbering), and this is stabilized by the silicon unit, but it is not clear why in some cases (see Table 1) a proton is lost rather than the trimethylsilyl group. Likewise, the stereochemical outcome – OH and SiMe₃ syn and OH axial – for **28** and **37** is also

difficult to interpret. However, we speculate that the following factors may play a role in determining the stereochemical results. It is reasonable to assume that the cyclization occurs via a chair-like transition state, and it is possible that both the carbonyl and the α oxygen substituent are protonated. In these circumstances an axial conformation of the carbonyl oxygen and the α substituent would minimize dipolar and steric interactions between the protonated oxygens. Such a conformation leads to the observed axial alcohol as product. Where an α substituent is not present, we again assume a chair-like transition state, and we suspect that the protonated or Lewis acid-complexed carbonyl still adopts an axial conformation so as to minimize steric interactions with the acetylenic unit.

We note that use of camphorsulfonic acid results in retention of the silicon group. The loss of the silicon unit in those cases where best yields are obtained by use of TBAF (Table 1, entries 4, 7, and 9) is expected, as the process would be initiated by F^- attack on silicon.³⁷

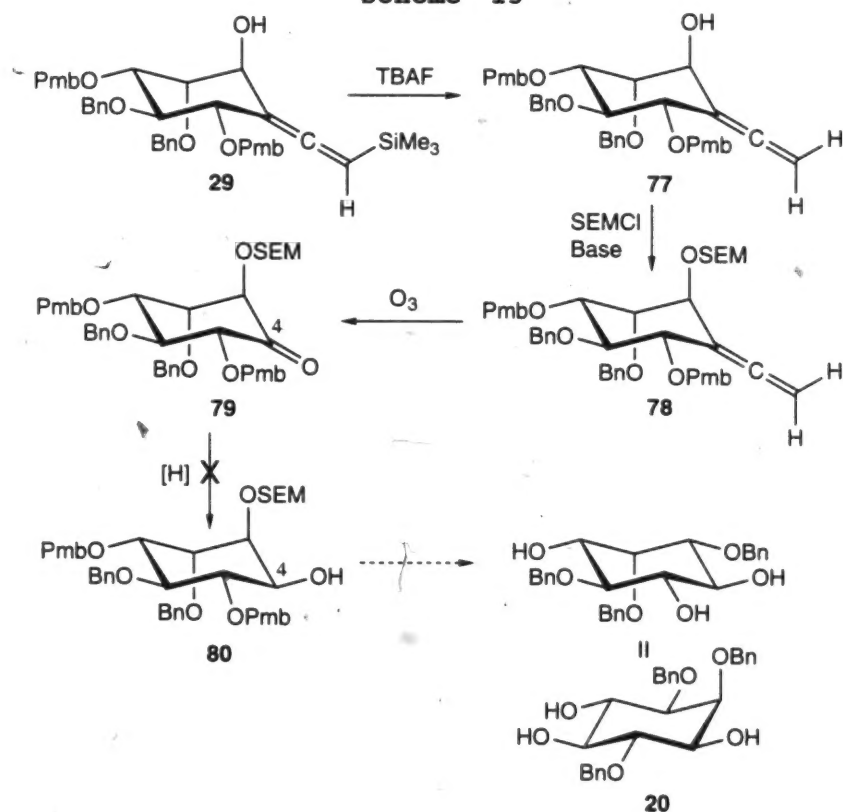
Although the mechanistic details are unclear, the cyclization of ω -formyl propargyl silanes represents a route to carbocycles that incorporate an allene³⁸ appendage; in favorable cases the yield is good and the reaction can be highly stereoselective.

2. Synthesis of 2,3,6-tri-O-benzyl-D-myo-inositol (20) from silyl allene (29)

In Postema's exploring work,¹⁷ the stereochemistry of silyl allene **29** was not established. After going through the standard transformations (desilylation with TBAF, oxidative cleavage of the exocyclic double bond with O_3 , reduction of the corresponding ketone with $NaBH_4$, and deprotection), the final product was found to differ from the target compound **20**.

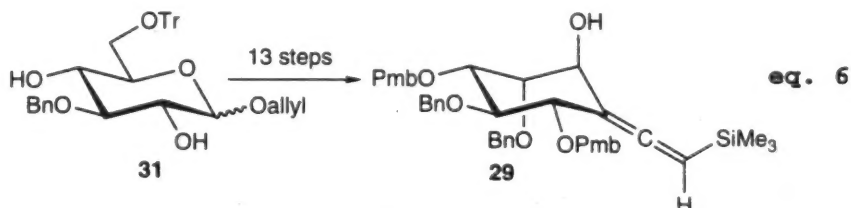
This synthetic study was then continued by Mashimbye.

Scheme 15



The synthetic route he followed is summarized in Scheme 15.³⁹ The strategy of this route was to get an equatorial hydroxyl at C(4) first. However, the desired stereoselective reduction of the carbonyl at C(4) could not be achieved.

Based on the above studies, we started with partially protected allyl glucopyranosides (**31**).⁴⁰ With some modification (see experimental section) we followed the prior methods developed in this laboratory, and prepared key intermediate **29** in 13 steps, the overall yield of **29** from **31** being 26% (see eq. 6 and Scheme 6 for reaction details). The stereochemistry of **29** could be assigned by comparison with the corresponding all-benzyl analog (**37a**), as mentioned earlier.



After protection of the hydroxyl at C(3), we examined the oxidative cleavage of the corresponding fully protected compound **81**, since desilylation of allenic silane with TBAF gave low yield. However, all our attempts were unsuccessful (Table 2) and our experiments suggested that the allenic silyl group should be removed first.

We next examined various methods to remove the silicon group (**81** → **82**, eq. 8), choosing conditions that work with

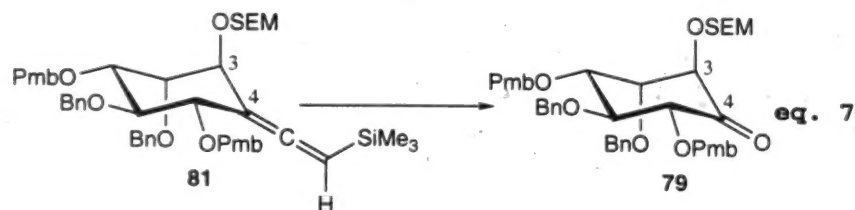
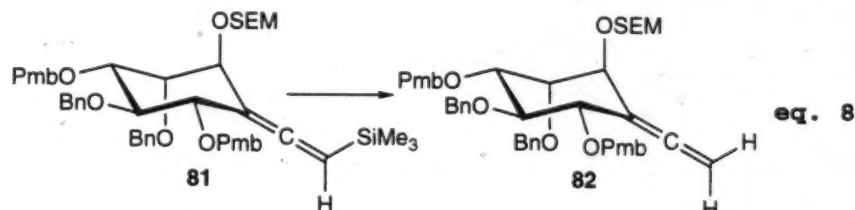
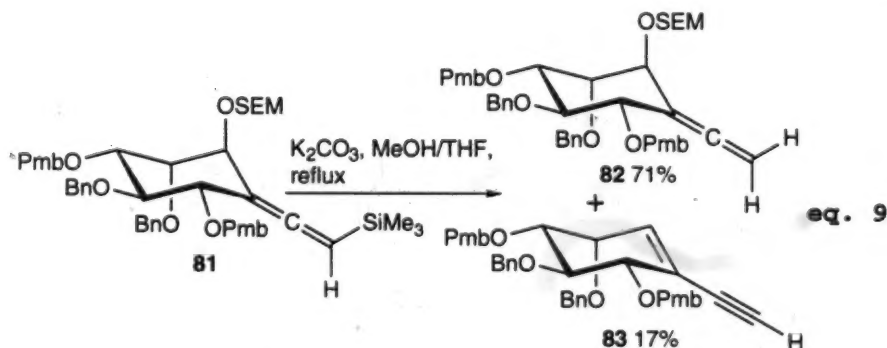
Table 2. Attempted oxidative cleavage of **81**

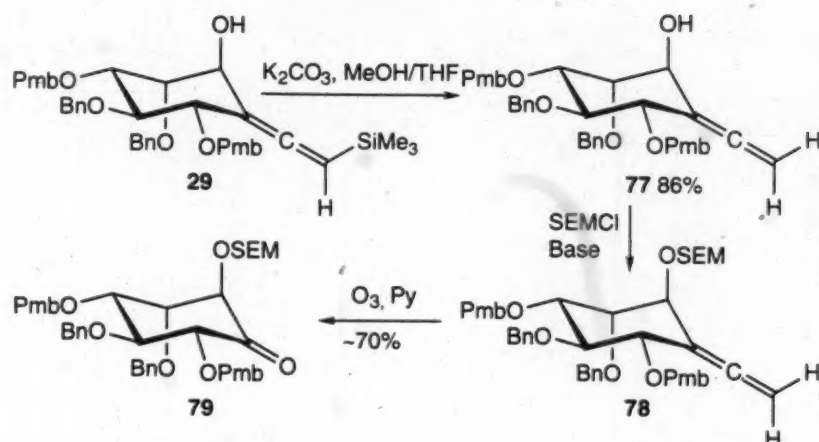
Table 3. Attempted desilylation of **81**

Condition	Result (yield)
TsOH, MeCN/THF/H ₂ O reflux	complex mixture
AcOH/THF/H ₂ O rt	No reaction
K ₂ CO ₃ , MeOH/THF reflux	82 (71%) 83 (17%)



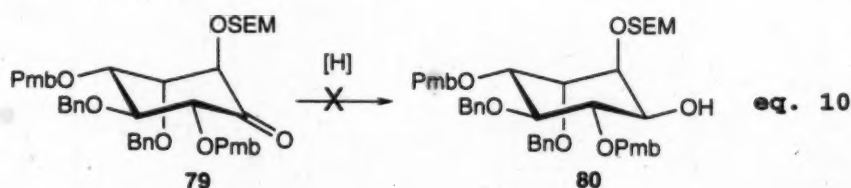
Following protection of the hydroxyl at C(3) (**77** → **78**), allene **78** was submitted to oxidative cleavage conditions. Osmylation or ruthenium tetroxide-catalyzed oxidation^{27a} again gave no desired product. Ozonolysis of **78** afforded **79** in ~70% yield, when done under optimum conditions. The amount of ozone used was important in this transformation, as

Scheme 16



an excess of ozone leads to a very poor yield. Presumably, the *p*-methoxybenzyl groups are oxidized by excess of ozone, and it is also possible that the desired ketone enolizes in situ, and then reacts further with ozone.

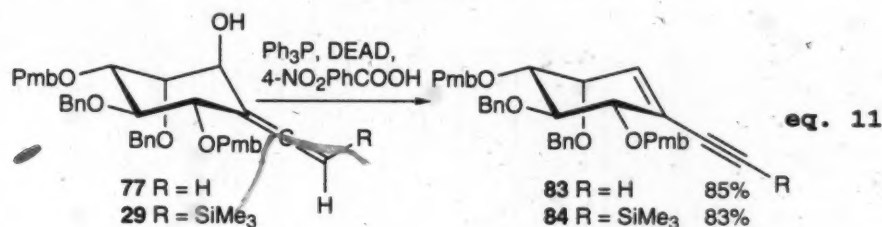
Reduction of **79** to equatorial alcohol **80** (eq. 10) was unsuccessful by using $NaBH_4$, $NaBH_4-CeCl_3$ ⁴¹ or Meerwein-Ponndorf-Verley reaction [$Al(Oi-Pr)_3$ -*i*-PrOH; $Gd(Oi-Pr)_3$ -*i*-PrOH⁴²]. With the hydride reagents only the axial alcohol was obtained, and under conditions of the Meerwein-Ponndorf-Verley reaction we recovered starting material from a complex mixture of products.



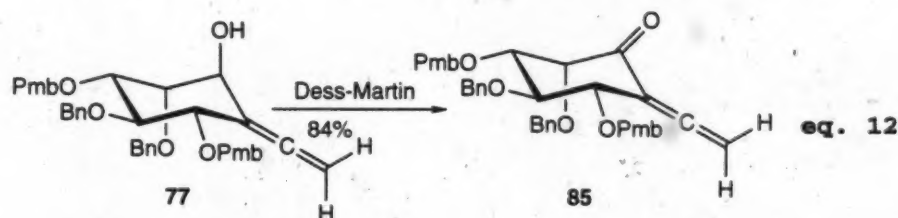
Attempts to invert the C(4) center of axial hydroxyl isomer of **80**, by either Mitsunobu reaction or formation of the corresponding triflate, followed by displacement with

acetate, were also not successful. Indeed, displacements adjacent to axial oxygen substituents in a six-membered ring are known to be difficult.⁴³

At this point we decided to try to invert the C(3) center. However, when allenes **29** and **77** were individually subjected to Mitsunobu conditions (eq. 11), elimination occurred (cf. **81** $\rightarrow$ **83**, **41** $\rightarrow$ **41d**, **43** $\rightarrow$ **43b**) and the conjugated enynes **83** and **84** were formed. Evidently, elimination is faster than displacement.



We next used an oxidation-reduction process to invert the C(3) stereochemistry. Several reagents, including MnO₂, PDC, PCC, Swern, and TPAP-NMO, were tried to affect oxidation of **77**. Unfortunately, all these experiments gave none of the required product. However, this oxidation was finally

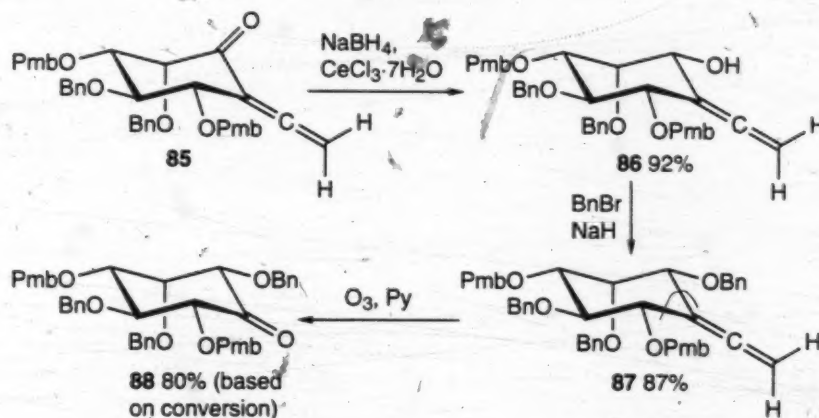


achieved with the Dess-Martin reagent in CH₂Cl₂, and gave ketone **85** in 84% yield (eq. 12).

Exposure of **85** to Luche's reagent⁴⁴ at a low temperature (-78 to 0 °C) afforded the required equatorial alcohol **86**,

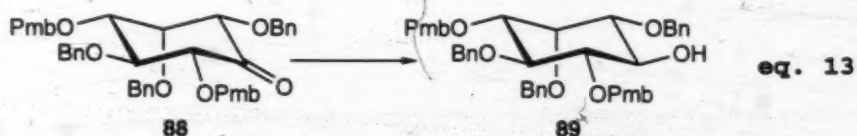
which was easily benzylated to give the fully protected allene **87** (Scheme 17). Ozonolysis of allene **87** was

Scheme 17



carried out with careful control. Our optimized procedure calls for a deficiency of O_3 in CH_2Cl_2 -pyridine at -78°C .⁴⁵ This procedure allows isolation of ketone **88** in 80% yield [after correction for recovered **87** (27%)].

Reduction of **88** in the correct stereochemical sense (to the equatorial alcohol **89**) required a good deal of effort, as

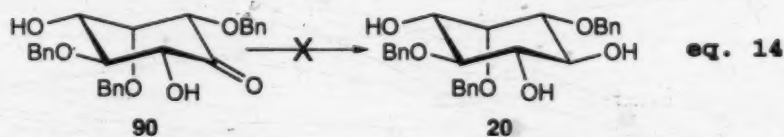
Table 4. Attempted stereoselective reduction of **88**

Reagent	Result
NaBH_4	ax alcohol

DIBAL	ax alcohol
MAD, <i>t</i> -BuMgCl ⁴⁶	starting material + complex mixture
MAD, DIBAL	ax alcohol
MAD, <i>n</i> -Bu ₄ NBH ₄	ax alcohol
MAD, NaBH ₄	ax alcohol
BH ₃ ·Me ₂ S	No reaction
SmI ₂ , <i>i</i> -PrOH ⁴⁷	complex mixture
Al(Oi-Pr) ₃ , <i>i</i> -PrOH	complex mixture
Sc(Oi-Pr) ₃ , <i>i</i> -PrOH ⁴⁸	No reaction
Ce(Oi-Pr) ₃ , <i>i</i> -PrOH ⁴⁹	complex mixture
(Ph ₃ P) ₃ RhCl, Et ₃ SiH ⁵⁰	No reaction

formation of the undesired axial alcohol was observed with all the conventional hydride reducing agents we tried (Table 4).

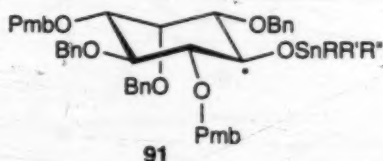
With the hope that an α -hydroxyl would control the stereoselectivity,⁵¹ we removed the Pmb ether groups with DDQ, and then treated the corresponding α -hydroxy ketone **90**.



with $\text{NaBH}(\text{OAc})_3$ in anhydrous HOAc (eq. 14). This experiment gave only trace amounts of the desired product **20**. With TFA as a medium instead of HOAc , the reaction gave a complex mixture, and no **20** was detected.

All these disappointing results led us to examine the possibility of inverting the axial into an equatorial alcohol. However, attempts to do so proved fruitless: Mitsunobu reaction did not proceed; displacement of the corresponding triflate group with acetate, trifluoroacetate, or potassium superoxide⁵² gave none (or only a trace) of the required product. The best result - 40% yield of desired product **89** - was achieved when we treated the triflate with KNO_2 and 18-crown-6 in DMF, followed by reflux in H_2O .⁵³ The failure of the Mitsunobu reaction may be understandable as follows. Possibly, the hydroxyl is too hindered (because of the presence of an axial benzyloxy group) to react with the Mitsunobu intermediate formed from the phosphine and diethyl azodicarboxylate. Had reaction occurred, the resulting species would be very likely to have reacted further, in the desired sense, as such a process would result in the relief of steric compression.

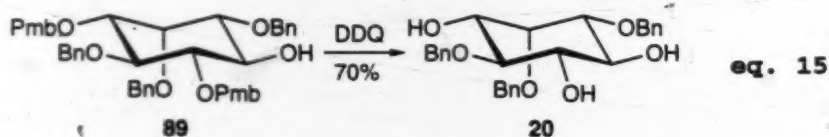
We were eventually led to consider a stannane-based



method for reduction, because we expected the intermediate radical⁵⁴ (see **91**) to abstract hydrogen where in the

conformation shown (with the bulky OSnR_3 -group equatorial). Examination of the literature on the stannane reduction of ketones brought to our attention the use of Bu_2SnHCl ⁵⁵ for reduction of α -alkoxy cyclohexanones to equatorial alcohols. The reagent is generated *in situ* from Bu_2SnH_2 and Bu_2SnCl_2 .⁵⁶ An equilibrium is, apparently, set up with Bu_2SnHCl .⁵⁷ When we used this reagent system in THF at room temperature, we obtained a 1:2 ratio of equatorial to axial alcohols. In refluxing THF the ratio improved to 2:1 in favor of the desired equatorial alcohol, but in refluxing PhMe, only the equatorial alcohol was formed (**88** $\rightarrow$ **89**, 88%). The mechanism of reduction by Bu_2SnHCl has been suggested⁵⁸ to involve a radical process, but the reagent is known⁵⁹ to reduce α -(phenylseleno) ketones (albeit in very poor yield) with preservation of the phenylseleno group, and this behavior suggests that, at least in those reactions, a radical mechanism is not involved (because phenylseleno groups are very easily removed by stannane reduction via a radical mechanism). The effect of solvent and temperature may reflect the operation of competing ionic and radical mechanisms.

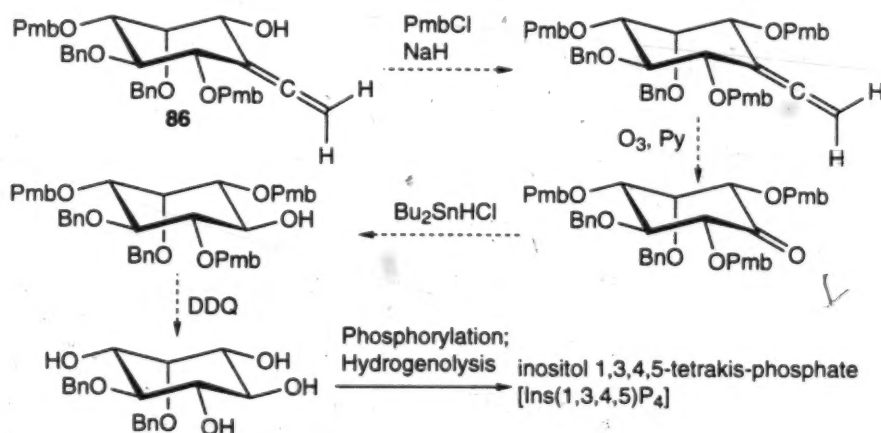
Finally, having reached **89**, oxidative removal of the *p*-methoxybenzyl groups (eq. 15) gave the target compound (**20**),



which is convertible¹² by phosphorylation and deprotection into D-myoinositol-1,4,5-tris(dihydrogenphosphate) (1).

In principle, other inositol phosphates⁶⁰ may be accessible by the method described here (e.g., Ins(1,3,4,5)P₄, whose potassium salt costs C\$ 501.90 per 100µg,⁶¹ see Scheme 18), but we have not tested this

Scheme 18



possibility. The outcome of any such attempts would depend on the generality of both the ene cyclization for other oxygenated acetylenes and the stereochemical outcome of the stannane reduction.

Conclusion

Based on the result that D-glucose was converted into the propargyl silane aldehyde 28 which, on treatment with camphorsulfonic acid, cyclized with retention of silicon, the allenic product 29 was obtained and elaborated via ketone 88 into 20, which had previously been converted into D-myoin-

inositol-1,4,5-tris(dihydrogenphosphate). Selective reduction of the advanced intermediate **88** was accomplished with $\text{Bu}_2\text{SnCl}_2/\text{Bu}_2\text{SnH}_2$, a reagent mixture that shows a very strong preference for generating equatorial alcohols. The cyclization step leading to allene **29** was studied by examining a number of model compounds; the unusual retention of silicon appears to be limited to highly oxygenated substrates, such as **28** and its all benzyl analog **37**.

Experimental

General Procedure. Unless stated to the contrary, the following conditions apply: Reactions were carried out under a slight static pressure of Ar that had been purified by passage through a column (3.5 x 42 cm) of R-311 catalyst⁶² and then through a similar column of Drierite. All solvents for reactions were dried, as described below. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexane used for chromatography was distilled before use.

Products were isolated from solution by evaporation under water aspirator vacuum at room temperature, using a rotary evaporator.

Microliter syringes were washed with water and acetone, using a suction device to draw the solvents through. Then air was sucked through for 1 min. The solution to be dispensed was drawn up and expelled, and this operation was repeated several times before drawing up the sample to be used. Cannula transfers were always done under slight pressure (Ar), not by suction.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F-254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic

acid,⁶³ followed by charring on a hot plate, or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by dry syringes fitted with oven-dried needles, or by cannula. Dry tetrahydrofuran (THF), Et₂O, and PhMe were distilled from sodium benzophenone ketyl. Dry Et₃N, *i*-Pr₂NH, CH₂Cl₂, and pyridine were distilled from CaH₂. HMPA was distilled from CaH₂ under reduced pressure (oil pump), and kept under Ar atmosphere over molecular sieves. All other solvents were used as purchased. Commercial (Aldrich) solutions of *n*-BuLi (in hexanes) were assumed to have the stated molarity.

FT-IR measurements were recorded on a Nicolet 7000 FTIR instrument. Measurements were made as casts from the specified solvent using potassium bromide plates.

¹H nuclear magnetic resonance spectra were recorded with Bruker AM-300 (at 300 MHz), Varian INOVA-300 (at 300 MHz), Bruker AM-360 (at 360 MHz) or Bruker AM-400 (at 400 MHz) spectrometers in the specified deuterated solvent. ¹³C spectra were recorded with Bruker AM-300 (at 75.5 MHz) or Varian UNITY-500 (at 125 MHz). The symbols s', d', t', and q' used for ¹³C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively, which are assigned based on the APT experiment.

Mass spectra were recorded with AEI Models MS-12, MS-50 MS9 (modified), Kratos MS50 (modified) or Micromass ZabSpec

Hybrid Sector-TOF mass spectrometers. For isotope peaks, high-resolution mass data were taken from the highest mass number peak shown in the spectrum.

Microanalyses were performed by the microanalytical laboratory of this Department. Compounds isolated by flash chromatography were homogeneous by TLC and, unless otherwise stated, were pure as judged by high field ^1H NMR spectra.

2-Propenyl 2,3,4-Tris-O-(phenylmethyl)-6-O-(triphenylmethyl)- β -D-glucopyranose (46).



Triol **45**³¹ (17.2 g, 37.2 mmol), powdered NaOH (30 g, 0.75 mol), and BnCl (200 mL, 1.74 mol) were heated at 120 °C with mechanical stirring for 1 h. Another portion of powdered NaOH (30 g, 0.75 mol) was then added and stirring and heating were continued for 36 h. The mixture was cooled, diluted with water (200 mL), and extracted with Et₂O (4 x 200 mL). The combined organic extracts were washed with brine (200 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (8 x 24 cm), using 1:10 EtOAc-hexane, gave **46** (23.8 g, 87%) as a pure (^1H NMR, 400 MHz) solid: FTIR (CH₂Cl₂ cast) unexceptional; ^1H NMR (CDCl₃, 400 MHz) δ 3.27 (dd, J = 9.3, 3.6 Hz, 1 H), 3.37–3.47 (m, 1 H), 3.54–3.68 (m, 3 H), 3.76–3.89 (m, 1 H), 4.28 (dd, J = 10.6, 4.6

Hz, 1 H), 4.40 (d, $J = 9.3$ Hz, 1 H), 4.48-4.60 (m, 2 H), 4.73 (d, $J = 9.6$ Hz, 1 H), 4.76-4.86 (m, 2 H), 4.94 (d, $J = 9.9$ Hz, 1 H), 5.05 (d, $J = 9.9$ Hz, 1 H), 5.27 (d, $J = 9.6$ Hz, 1 H), 5.43 (d, $J = 16.6$ Hz, 1 H), 6.00-6.13 (m, 1 H), 6.84-6.97 (m, 2 H), 7.10-7.48 (m, 22 H), 7.48-7.66 (m, 6 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 62.49 (t'), 70.10 (t'), 74.66 (d'), 74.98 (t'), 75.03 (t'), 75.95 (t'), 77.95 (d'), 82.61 (d'), 84.78 (d'), 86.41 (s'), 102.75 (d'), 117.41 (t'), 126.97 (d'), 127.26 (d'), 127.68 (d'), 127.81 (d'), 127.94 (d'), 128.06 (d'), 128.17 (d'), 128.22 (d'), 128.42 (d'), 128.87 (d'), 134.23 (d'), 137.92 (s'), 138.63 (s'), 143.98 (s'); mass (FAB) m/z calcd for $\text{C}_{49}\text{H}_{48}\text{NaO}_6$ ($M + \text{Na}$) 755.3, found 755.3.

2,3,4-Tris-*O*-(phenylmethyl)-6-*O*-(triphenylmethyl)- β -D-glucopyranose (47).



DMSO (60.0 mL) was added in one portion to a stirred suspension of **46** (16.7 g, 22.8 mmol) and t -BuOK (10.0 g, 89.1 mmol). The mixture was stirred to dissolve the solids and was then heated at 100 °C for 1 h with continued stirring. The resulting solution was cooled to room temperature, poured into water (200 mL), and extracted with Et_2O (4 x 50 mL). The combined organic extracts were washed with water (1 x 40 mL) and evaporated. The solid residue was dissolved in 10:1

acetone-water (50 mL), and HgO (8.38 g, 38.7 mmol) was added (stirring). A solution of HgCl₂ (10.5 g, 38.7 mmol) in 10:1 acetone-water (20 mL) was added dropwise, and stirring was continued for 4 h. The mixture was filtered through a pad (5 x 4 cm) of Celite, using acetone (100 mL) as a rinse. The combined filtrates were evaporated and the residue was dissolved in Et₂O (200 mL), washed with 20% aqueous NaI (1 x 200 mL) and brine (100 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (8 x 25 cm), using 2:8 EtOAc-hexane, gave **47** (14.0 g, 88%) as a pure (¹H NMR, 300 MHz), gummy solid, which was a mixture of epimers: FTIR (CH₂Cl₂ cast) 3439 (br) cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 2.92 (br s, 0.66 H), 3.14 (br d, *J* = 5.3 Hz, 0.34 H), 3.23 (dd, *J* = 3.3, 3.3 Hz, 0.34 H), 3.26 (dd, *J* = 3.3, 3.3 Hz, 0.66 H), 3.43-3.75 (m, 2.66 H), 3.75-3.87 (m, 1 H), 3.95 (dd, *J* = 9.0, 9.0 Hz, 0.66 H), 4.06 (br d, *J* = 10.5 Hz, 0.66 H), 4.36 (d, *J* = 10.5, 1 H), 4.66-4.96 (m, 5 H), 5.02 (d, *J* = 11.3 Hz, 0.34 H), 5.39 (dd, *J* = 2.8, 2.8 Hz, 0.66 H), 6.83-6.93 (m, 2 H), 7.12-7.42 (m, 22 H), 7.42-7.53 (m, 6 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 62.27 (t'), 62.61 (t'), 70.56 (d'), 73.26 (t'), 74.78 (t'), 74.89 (t'), 75.85 (t'), 75.94 (t'), 77.81 (d'), 80.48 (d'), 81.85 (d'), 83.41 (d'), 84.64 (d'), 86.33 (s'), 86.55 (s'), 91.23 (d'), 97.60 (d'), 126.93 (d'), 127.49 (d'), 127.58 (d'), 127.69 (d'), 127.79 (d'), 127.94 (d'), 128.06 (d'), 128.12 (d'), 128.14 (d'), 128.40 (d'), 128.42 (d'), 128.52 (d'), 128.81 (d'), 137.85 (s'), 138.02 (s'), 138.48 (s'), 138.59 (s'), 143.82 (s'), 143.90 (s');

mass (FAB) m/z calcd for $C_{46}H_{44}NaO_6$ ($M + Na$) 715.3, found 715.2. Anal. calcd for $C_{46}H_{44}O_6$: C, 79.73; H, 6.41. Found: C, 79.49; H, 6.50.

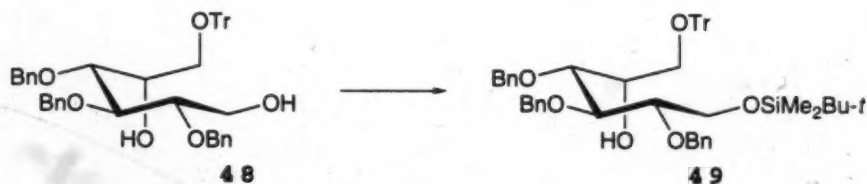
2,3,4-Tris-O-(phenylmethyl)-6-O-(triphenylmethyl)-D-glucitol (48).



$LiAlH_4$ (2.42 g, 63.8 mmol) was added in five portions to a stirred and cooled (0 °C) solution of **47** (16.9 g, 24.4 mmol) in THF (300 mL). The cold bath was removed, stirring was continued for 4 h, and the mixture was then cooled to 0 °C. Water (1.0 mL), 15% aqueous NaOH (1.0 mL), and water (1.0 mL) were added sequentially with stirring. The cold bath was removed, stirring was continued for 30 min, and the mixture was then filtered through a pad (8 x 3 cm) of Celite, using Et_2O (500 mL) as a rinse. Evaporation of the combined filtrates, and flash chromatography of the residue over silica gel (8 x 25 cm), using 3:7 EtOAc-hexane, gave **48** (16.2 g, 95%) as a pure (^1H NMR, 400 MHz) solid: $[\alpha]_D = 3.10$ (c 2.03, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3457 cm^{-1} ; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.09 (t, $J = 5.8$ Hz, 1 H), 3.09 (d, $J = 5.4$ Hz, 1 H), 3.32 (dd, $J = 9.6, 4.6$ Hz, 1 H), 3.37 (dd, $J = 9.6, 4.0$ Hz, 1 H), 3.53-3.61 (m, 1 H), 3.66-3.75 (m, 1 H), 3.76-3.84 (m, 2 H), 3.87 (dd, $J = 6.6, 2.6$ Hz, 1 H), 4.03-4.11 (m, 1

H), 4.42 (d, $J = 12.0$ Hz, 1 H), 4.45 (d, $J = 12.0$ Hz, 1 H), 4.53 (d, $J = 13.0$ Hz, 1 H), 4.61 (d, $J = 13.4$ Hz, 1 H), 4.66 (d, $J = 13.4$ Hz, 1 H), 4.68 (d, $J = 13.0$ Hz, 1 H), 7.07-7.16 (m, 2 H), 7.20-7.38 (m, 22 H), 7.40-7.51 (m, 6 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 61.88 (t'), 64.65 (t'), 70.72 (d'), 72.88 (t'), 73.03 (t'), 74.41 (t'), 76.96 (d'), 79.29 (d'), 79.46 (d'), 86.69 (s'), 127.08 (d'), 127.32 (d'), 127.76 (d'), 127.78 (d'), 127.85 (d'), 127.90 (d'), 127.94 (d'), 128.19 (d'), 128.23 (d'), 128.32 (d'), 128.34 (d'), 128.37 (d'), 128.44 (d'), 128.46 (d'), 128.73 (d'), 128.85 (d'), 128.87 (d'), 129.10 (d'), 137.64 (s'), 137.80 (s'), 138.19 (s'), 143.78 (s'); mass (FAB) m/z calcd for $\text{C}_{46}\text{H}_{46}\text{NaO}_6$ ($M + \text{Na}$) 717.3, found 717.2.

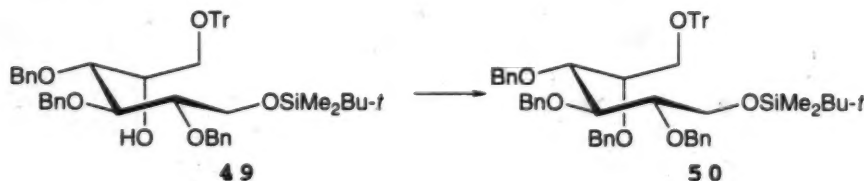
1-O-[(1,1-Dimethylethyl)dimethylsilyl]-2,3,4-tris-O-(phenylmethyl)-6-O-(triphenylmethyl)-D-glucitol (49).



Et_3N (5.13 mL, 36.8 mmol) was added in one portion to a stirred solution of **48** (16.1 g, 23.2 mmol), DMAP (710 mg, 5.81 mmol), and $t\text{-BuMe}_2\text{SiCl}$ (5.44 g, 36.1 mmol) in CH_2Cl_2 (500 mL). Stirring was continued for 16 h, CH_2Cl_2 (200 mL) was added, and the mixture was washed with brine (2 x 200 mL),

dried, and evaporated. Flash chromatography of the residue over silica gel (8 x 25 cm), using 1:10 EtOAc-hexane, gave **49** (18.3 g, 95%) as a pure (^1H NMR, 300 MHz), gummy solid: $[\alpha]_D = 3.35$ (c 1.55, CH_2Cl_2); FTIR (CH_2Cl_2 cast) unexceptional; ^1H NMR (CDCl_3 , 300 MHz) δ 0.02 (s, 6 H), 0.90 (s, 9 H), 3.11 (dd, $J = 4.9, 1.2$ Hz, 1 H), 3.27-3.42 (m, 2 H), 3.67-3.84 (m, 4 H), 3.84-3.93 (m, 1 H), 3.98-4.10 (m, 1 H), 4.44 (d, $J = 11.4$ Hz, 1 H), 4.47 (d, $J = 11.4$ Hz, 1 H), 4.54 (d, $J = 11.0$ Hz, 1 H), 4.63 (d, $J = 11.2$ Hz, 2 H), 4.73 (d, $J = 11.0$ Hz, 1 H), 7.04-7.16 (m, 2 H), 7.16-7.40 (m, 22 H), 7.40-7.56 (m, 6 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ -5.39 (q'), -5.35 (q'), 18.20 (s'), 25.94 (q'), 63.23 (t'), 64.87 (t'), 71.13 (d'), 72.97 (t'), 73.21 (t'), 74.09 (t'), 77.22 (d'), 78.33 (d'), 79.81 (d'), 86.61 (s'), 126.99 (d'), 127.49 (d'), 127.70 (d'), 127.80 (d'), 127.95 (d'), 128.03 (d'), 128.17 (d'), 128.19 (d'), 128.29 (d'), 128.35 (d'), 128.76 (d'), 138.09 (s'), 138.12 (s'), 138.59 (s'), 143.96 (s'); mass (FAB) m/z calcd for $\text{C}_{52}\text{H}_{60}\text{NaO}_6\text{Si}$ ($M + \text{Na}$) 831.4, found 831.4. Anal. Calcd for $\text{C}_{52}\text{H}_{60}\text{O}_6\text{Si}$: C, 77.19; H, 7.48. Found: C, 77.08; H, 7.58.

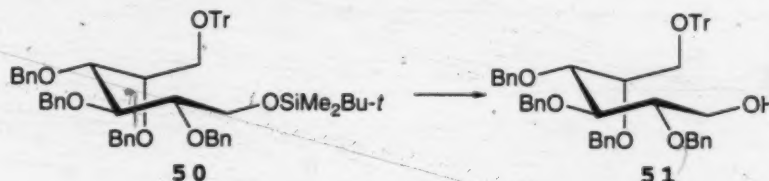
1-O-[(1,1-Dimethylethyl)dimethylsilyl]-2,3,4,5-tetrakis-O-(phenylmethyl)-6-O-(triphenylmethyl)-D-glucitol (50).



NaH (80% dispersion in oil, 1.48 g, 49.3 mmol) was added in six portions to a stirred and cooled (0 °C) solution of **49** (18.2 g, 22.5 mmol) in THF (400 mL). The resulting mixture was stirred for 30 min and then BnBr (5.88 mL, 49.4 mmol) was added neat in one portion. The cold bath was removed and the mixture was stirred for 1 h and then refluxed for 14 h. The resulting mixture was cooled (0 °C) and quenched with MeOH (60 mL), diluted with brine (200 mL), and extracted with Et₂O (3 x 500 mL). The combined organic extracts were washed with brine (1 x 150 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (8 x 25 cm) using 1:20 EtOAc-hexane, gave **50** (19.2 g, 94%) as a pure (¹H NMR, 300 MHz), thick syrup: $[\alpha]_D = -3.23$ (c 3.5, CH₂Cl₂); FTIR (CH₂Cl₂ cast) unexceptional; ¹H NMR (CDCl₃, 300 MHz) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.96 (s, 9 H), 3.47 (dd, $J = 10.2, 5.1$ Hz, 1 H), 3.66 (dd, $J = 10.0, 2.6$ Hz, 1 H), 3.71-3.84 (m, 3 H) 3.87-3.96 (m, 2 H), 4.17 (dd, $J = 5.5, 5.5$ Hz, 1 H), 4.47 (d, $J = 11.5$ Hz, 1 H), 4.61-4.73 (m, 5 H), 4.78 (d, $J = 11.5$ Hz, 1 H), 4.81 (d, $J = 11.7$ Hz, 1 H), 7.10-7.20 (m, 2 H), 7.20-7.46 (m, 27 H), 7.51-7.64 (m, 6 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ -5.38 (q'), 18.22 (s'), 25.98 (q'), 63.20 (t'), 63.96 (t'), 72.17 (t'), 73.18 (t'), 73.83 (t'), 74.46 (t'), 78.60 (d'), 79.56 (d'), 80.67 (d'), 86.82 (s'), 126.92 (d'), 127.22 (d'), 127.27 (d'), 127.33 (d'), 127.76 (d'), 127.91 (d'), 128.05 (d'), 128.12 (d'), 128.16 (d'), 128.23 (d'), 128.86 (d'), 138.72 (s'), 138.79 (s'), 138.84 (s'),

138.97 (s'), 144.11 (s'); mass (FAB) m/z calcd for $C_{59}H_{66}NaO_6Si$ ($M + Na$) 921.5, found 921.4.

2,3,4,5-Tetrakis-O-(phenylmethyl)-6-O-(triphenylmethyl)-D-glucitol (51).



TBAF (21.6 mL, 1 M in THF, 21.6 mmol) was added in one portion to a stirred solution of **50** (19.1 g, 21.3 mmol) in THF (410 mL). Stirring was continued for 4 h, the mixture was diluted with Et₂O (200 mL), and washed with water (1 x 150 mL). The aqueous phase was extracted with Et₂O (2 x 100 mL) and the combined organic extracts were washed with brine (1 x 150 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (8 x 20 cm), using 2:8 EtOAc-hexane, gave **51** (16.2 g, 97%) as a pure (¹H NMR, 400 MHz) solid: $[\alpha]_D = -9.08$ (c 9.08, CH₂Cl₂); FTIR (CH₂Cl₂ cast) 3457 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 2.08 (br s, 1 H), 3.42 (dd, $J = 10.2, 5.3$ Hz, 1 H), 3.57 (dd, $J = 10.2, 2.9$ Hz, 2 H), 3.65 (ddd, $J = 4.9, 4.9, 4.9$ Hz, 1 H), 3.68-3.77 (m, 1 H), 3.83-3.89 (m, 2 H), 4.05 (dd, $J = 4.9, 4.9$ Hz, 1 H), 4.43 (d, $J = 11.4$ Hz, 1 H), 4.54-4.64 (m, 6 H), 4.74 (d, $J = 11.4$ Hz, 1 H), 7.05-7.14 (m, 2 H), 7.18-7.40 (m, 26 H), 7.40-7.54 (m, 7 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 61.78 (t'), 62.96 (t'), 72.00 (t'), 72.33 (t'), 73.52 (t'), 74.26 (t'), 78.30 (d'), 78.96

(d'), 79.04 (d'), 79.07 (d'), 86.76 (s'), 126.80 (d'), 127.23 (d'), 127.41 (d'), 127.46 (d'), 127.61 (d'), 127.71 (d'), 127.74 (d'), 127.95 (d'), 128.12 (d'), 128.20 (d'), 128.63 (d'), 129.04 (d'), 138.17 (s'), 138.21 (s'), 138.43 (s'), 143.83 (s'); exact mass m/z calcd for $C_{34}H_{37}O_6$ (M - Ph_3C) 541.25903, found 541.25931. Anal. Calcd for $C_{53}H_{52}O_6$: C, 81.08; H, 6.68. Found: C, 81.06; H, 6.72.

2,3,4,5-Tetrakis-O-(phenylmethyl)-6-O-(triphenylmethyl)-D-glucose (52).



DMSO (1.05 mL, 14.8 mmol) was added dropwise to a stirred and cooled ($-78\text{ }^{\circ}\text{C}$) solution of $(COCl)_2$ (0.96 mL, 11.0 mmol) in CH_2Cl_2 (40 mL). After 20 min, **51** (2.89 g, 3.69 mmol) in CH_2Cl_2 (12 mL) was added by syringe over 1 min. Stirring was continued for 30 min at $-78\text{ }^{\circ}\text{C}$, and then Et_3N (4.11 mL, 29.5 mmol) was added dropwise over 2 min. The cold bath was removed and stirring was continued for 6 h. The solution was diluted with water (2 mL) and CH_2Cl_2 (50 mL), and the mixture was transferred to a separatory funnel. The organic phase was washed with brine (1 x 30 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (3 x 25 cm), using 1:10 to 2:8 EtOAc-hexane, gave **52** (2.56 g, 89%) as a pure (^1H NMR, 300 MHz) solid: $[\alpha]_D =$

-3.64 (c 0.44, CH₂Cl₂); FTIR (CH₂Cl₂ cast) 1728 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 3.36 (dd, *J* = 10.2, 4.2 Hz, 1 H), 3.73 (dd, *J* = 10.0, 2.4 Hz, 1 H), 3.83-3.91 (m, 1 H), 3.92 (d, *J* = 5.0 Hz, 1 H), 4.15-4.25 (m, 2 H), 4.36-4.62 (m, 6 H), 4.81 (d, *J* = 11.8 Hz, 1 H), 4.85 (d, *J* = 11.8 Hz, 1 H), 6.88-6.98 (m, 2 H), 7.10-7.29 (m, 18 H), 7.31-7.42 (m, 9 H), 7.44-7.54 (m, 6 H), 9.72 (s, 1 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 62.57 (t'), 72.18 (t'), 73.15 (t'), 73.37 (t'), 73.99 (t'), 76.82 (d'), 78.67 (d'), 79.99 (d'), 81.18 (d'), 86.85 (s'), 127.00 (d'), 127.27 (d'), 127.33 (d'), 127.46 (d'), 127.83 (d'), 128.00 (d'), 128.11 (d'), 128.36 (d'), 128.51 (d'), 128.81 (d'), 137.48 (s'), 137.72 (s'), 137.82 (s'), 138.53 (s'), 143.93 (s'), 200.79 (d'); mass (FAB) *m/z* calcd for C₅₃H₅₀NaO₆ (M + Na) 805.4, found 805.4. Anal. Calcd for C₅₃H₅₀O₆: C, 81.29; H, 6.44. Found: C, 81.25; H, 6.24.

1,1-Dibromo-1,2-dideoxy-3,4,5,6-tetrakis-O-(phenylmethyl)-7-O-(triphenylmethyl)-D-gluco-hept-1-enitol (53),



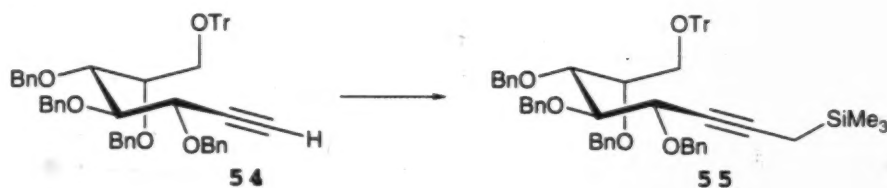
A solution of CBr₄ (1.22 g, 3.68 mmol) in CH₂Cl₂ (20 mL) was added at a fast dropwise rate to a stirred and cooled (-20 °C) solution of Ph₃P (0.96 g, 3.66 mmol) in CH₂Cl₂ (20 mL). Stirring at -20 °C was continued for 15 min, and then a

solution of **52** (1.44 g, 1.84 mmol) and Et_3N (0.26 mL, 1.87 mmol) in CH_2Cl_2 (20 mL) was added dropwise at -60°C . The cold bath was removed, stirring was continued for 30 min, and the mixture was filtered through a pad (3 x 3 cm) of flash chromatography silica gel, using Et_2O (50 mL) as a rinse.

Evaporation of the combined filtrates, and flash chromatography of the residue over silica gel (1.5 x 20 cm), using 1:9 EtOAc-hexane, gave **53** (1.31 g, 76%) as a pure (^1H NMR, 200 MHz), gummy solid: $[\alpha]_D = 6.02$ (c 0.98 CH_2Cl_2); FTIR (CH_2Cl_2 cast) unexceptional; ^1H NMR (CDCl_3 , 200 MHz) δ 3.46 (d, $J = 4.0$ Hz, 2 H), 3.69-3.86 (m, 2 H), 4.14 (dd, $J = 5.1$, 5.1 Hz, 1 H), 4.30 (dd, $J = 7.9$, 4.0 Hz, 1 H), 4.42 (d, $J = 11.7$ Hz, 1 H), 4.47 (d, $J = 11.5$ Hz, 1 H), 4.55-4.82 [m, 6 H, including doublet at δ 4.75 ($J = 11.5$ Hz, 1 H)], 6.66 (d, $J = 7.9$ Hz, 1 H), 7.05-7.18 (m, 2 H), 7.18-7.42 (m, 27 H), 7.42-7.59 (m, 6 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 63.13 (t'), 71.30 (t'), 72.43 (t'), 74.22 (t'), 74.99 (t'), 78.77 (d'), 79.48 (d'), 79.72 (d'), 86.76 (s'), 92.63 (s'), 126.95 (d'), 127.30 (d'), 127.42 (d'), 127.46 (d'), 127.60 (d'), 127.80 (d'), 128.01 (d'), 128.11 (d'), 128.18 (d'), 128.24 (d'), 128.32 (d'), 128.43 (d'), 128.90 (d'), 137.32 (d'), 137.62 (s'), 138.31 (s'), 138.60 (s'), 138.69 (s'), 144.02 (s'); mass (FAB) m/z calcd for $\text{C}_{54}\text{H}_{50}^{79}\text{Br}^{81}\text{BrNaO}_5$ ($M + \text{Na}$) 961.2, found 961.6.

(d'), 78.69 (d'), 80.91 (s'), 81.05 (d'), 86.68 (s'), 126.95 (d'), 127.25 (d'), 127.34 (d'), 127.78 (d'), 128.01 (d'), 128.04 (d'), 128.11 (d'), 128.24 (d'), 128.30 (d'), 128.39 (d'), 128.86 (d'), 137.54 (s'), 138.48 (s'), 138.67 (s'), 138.95 (s'), 144.08 (s'); mass (FAB) m/z calcd for $C_{54}H_{50}O_5$ 779.0, found 778.9.

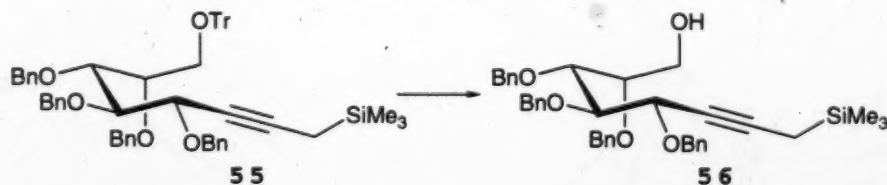
1,2,3-Trideoxy-4,5,6,7-tetrakis-*O*-(phenylmethyl)-1-(trimethylsilyl)-8-*O*-(triphenylmethyl)-*D*-gluco-oct-2-ynitol (55).



n-BuLi (2.5 M in hexane, 0.29 mL, 0.725 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **54** (0.509 g, 0.654 mmol) in THF (20 mL). Stirring at -78 °C was continued for 1 h, and then $Me_3SiCH_2OSO_2CF_3$ (0.17 mL, 0.850 mmol) and HMPA (0.40 mL, 2.30 mmol) were added rapidly, each in one portion. The cold bath was removed and stirring was continued for 10 h. The mixture was diluted with Et_2O (20 mL) and washed with brine (1 x 20 mL). The aqueous phase was extracted with Et_2O (2 x 20 mL) and the combined organic extracts were dried and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 1:10 $EtOAc$ -hexane, gave **55** (0.441 g, 78%) as a pure (^1H NMR, 300 MHz) solid: FTIR (CH_2Cl_2 cast) unexceptional; ^1H NMR ($CDCl_3$, 300

MHz) δ 0.27 (s, 9 H), 1.73 (dd, $J = 1.9, 1.9$ Hz, 2 H), 3.36
 (dd, $J = 10.2, 4.4$ Hz, 1 H), 3.74 (dd, $J = 10.2, 2.0$ Hz, 1
 H), 3.92-4.01 (m, 1 H), 4.13 (dd, $J = 7.6, 3.5$ Hz, 1 H), 4.38
 (d, $J = 11.7$ Hz, 1 H), 4.47 (dd, $J = 7.6, 2.8$ Hz, 1 H), 4.52-
 4.67 [m, 4 H, including doublet at δ 4.56 ($J = 11.0$ Hz, 1
 H)], 4.71 (d, $J = 11.0$ Hz, 1 H), 4.81 (d, $J = 11.7$ Hz, 1 H),
 4.95 (d, $J = 11.6$ Hz, 1 H), 5.04 (d, $J = 11.7$ Hz, 1 H), 7.02-
 7.12 (m, 2 H), 7.20-7.50 (m, 27 H), 7.50-7.62 (m, 6 H); ^{13}C
 NMR (CDCl_3 , 75.5 MHz) δ -1.76 (q'), 7.44 (t'), 62.67 (t'),
 71.03 (t'), 71.85 (s'), 72.40 (d'), 74.68 (t'), 74.72 (t'),
 75.85 (t'), 78.51 (d'), 79.09 (d'), 81.75 (d'), 86.68 (s'),
 87.02 (s'), 126.91 (d'), 127.11 (d'), 127.19 (d'), 127.21
 (d'), 127.23 (d'), 127.56 (d'), 127.72 (d'), 127.76 (d'),
 127.99 (d'), 128.02 (d'), 128.08 (d'), 128.21 (d'), 128.25
 (d'), 128.33 (d'), 128.91 (d'), 138.16 (s'), 138.68 (s'),
 138.86 (s'), 139.34 (s'), 144.19 (s'); exact mass m/z calcd
 for $\text{C}_{32}\text{H}_{37}\text{O}_4\text{Si}$ (M - H - Ph_3C - OBn) 513.24609, found
 513.24569.

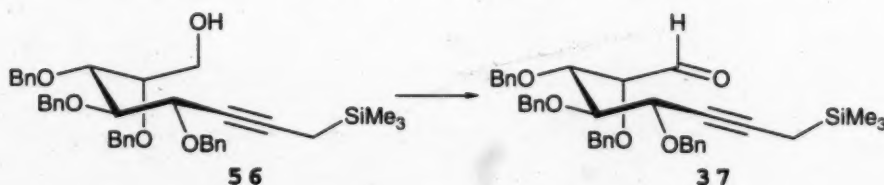
1,2,3-Trideoxy-4,6,5,7-tetrakis-O-(phenylmethyl)-
1-(trimethylsilyl)-D-gluco-oct-2-ynitol (56).



CSA (12.0 mg, 0.052 mmol) in MeOH (2 mL) was added in one portion to a stirred solution of **55** (0.409 g, 0.473 mmol)

in CH_2Cl_2 (20 mL). Stirring was continued for 24 h, Et_3N (1 mL) was added, and the solution was evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 2:8 EtOAc-hexane, gave **56** (0.276 g, 94%) as a pure (^1H NMR, 300 MHz), thick syrup: FTIR (CH_2Cl_2 cast) 3474, 2212 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.19 (s, 9 H), 1.62 (dd, $J = 2.3$, 2.3 Hz, 2 H), 2.08 (br s, 1 H), 3.73-3.86 (m, 2 H), 3.87-3.97 (m, 2 H), 4.21-4.28 (m, 1 H), 4.37 (d, $J = 11.5$ Hz, 1 H), 4.48-4.68 (m, 4 H), 4.79 (d, $J = 2.5$ Hz, 2 H), 4.90 (dd, $J = 11.5$, 2.5 Hz, 1 H), 5.00 (dd, $J = 11.7$, 2.2 Hz, 1 H), 7.19-7.44 (m, 20 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ -1.79 (q'), 7.44 (t'), 60.34 (t'), 71.05 (t'), 71.35 (t'), 72.12 (d'), 74.70 (t'), 75.22 (t'), 75.40 (s'), 79.15 (d'), 79.31 (d'), 81.56 (d'), 87.24 (s'), 127.42 (d'), 127.55 (d'), 127.58 (d'), 127.66 (d'), 127.69 (d'), 128.01 (d'), 128.05 (d'), 128.12 (d'), 128.23 (d'), 128.30 (d'), 128.39 (d'), 128.44 (d'), 138.00 (s'), 138.30 (s'), 138.51 (s'), 138.91 (s'); exact mass m/z calcd for $\text{C}_{25}\text{H}_{31}\text{O}_4\text{Si}$ (M - H - Bn - OBn) 423.19916, found 423.19960.

6,7,8-Trideoxy-2,3,4,5-tetrakis-O-(phenylmethyl)-8-(trimethylsilyl)-L-gulo-oct-6-ynose (37).



DMSO (0.14 mL, 1.97 mmol) was added dropwise to a stirred and cooled solution (-78 °C) of (COCl)₂ (0.13 mL, 1.49 mmol) in CH₂Cl₂ (10 mL). After 20 min, **56** (0.302 g, 0.486 mmol) in CH₂Cl₂ (5 mL) was added by syringe over 1 min. Stirring was continued for 30 min at -78 °C, and then Et₃N (0.54 mL, 3.86 mmol) was added dropwise over 2 min. After a further 30 min, the cold bath was removed and stirring was continued for 6 h. The mixture was diluted with water (2 mL) and CH₂Cl₂ (15 mL), and transferred to a separatory funnel. The organic phase was washed with brine (20 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 1:10 to 2:8 EtOAc-hexane, gave **37** (0.253 g, 84%) as a pure (¹H NMR, 360 MHz), colorless oil: FTIR (CH₂Cl₂ cast) 2213, 1735 cm⁻¹; ¹H NMR (CDCl₃, 360 MHz) δ 0.17 (s, 9 H), 1.58 (d, *J* = 2.1 Hz, 2 H), 3.89 (dd, *J* = 6.9, 3.5 Hz, 1 H), 4.08 (dd, *J* = 4.3, 1.6 Hz, 1 H), 4.29 (d, *J* = 11.4 Hz, 1 H), 4.31 (dd, *J* = 4.3, 4.3 Hz, 1 H), 4.49-4.70 (m, 6 H), 4.87 (d, *J* = 11.4 Hz, 1 H), 4.94 (d, *J* = 11.2 Hz, 1 H), 7.23-7.38 (m, 20 H), 9.69 (d, *J* = 1.4 Hz, 1 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ -1.79 (q'), 7.39 (t'), 71.00 (t'), 71.75 (d'), 72.35 (t'), 74.63 (t'), 75.04 (t'), 75.10 (s'), 80.85 (d'), 81.48 (d'), 83.89 (d'), 87.21 (s'), 127.62 (d'), 127.69 (d'), 127.83 (d'), 127.88 (d'), 128.13 (d'), 128.21 (d'), 128.28 (d'), 128.39 (d'), 128.43 (d'), 137.50 (s'), 137.92 (s'), 138.43 (s'), 201.27 (d'); exact mass *m/z* calcd for C₃₉H₄₄O₅Si 620.29578, found 620.29554.

Trimethyl[7-[(tetrahydro-2H-pyran-2-yl)oxy]-1-heptynyl]silane (58).



n-BuLi (2.5 M in hexane, 2.52 mL, 6.30 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of trimethylsilylacetylene (0.647 g, 6.60 mmol) in THF (20 mL). Stirring at -78 °C was continued for 15 min, and then a mixture of **57**³² (1.51 g, 6.01 mmol) and HMPA (1.5 mL, 8.63 mmol) was added in one portion. The cold bath was removed and stirring was continued for 15 h. The mixture was then quenched with saturated aqueous NH₄Cl (20 mL) at -78 °C, and extracted with hexane (3 x 20 mL). The combined organic extracts were washed with water (15 mL) and brine (20 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 1:10 EtOAc-hexane, gave **58** [0.975 g, 94% after correction for recovered **57** (35%)] as a pure (¹H NMR, 200 MHz), colorless oil: FTIR (CH₂Cl₂ cast) 2175 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz), δ 0.11 (s, 9 H), 1.35-1.90 (m, 12 H), 2.21 (t, *J* = 6.8 Hz, 2 H), 3.38 (dt, *J* = 9.6, 6.2 Hz, 1 H), 3.42-3.54 (m, 1 H), 3.72 (dt, *J* = 9.6, 6.2 Hz, 1 H), 3.77-3.90 (m, 1 H), 4.56 (dd, *J* = 3.6, 3.6 Hz, 1 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 0.15 (q'), 19.62 (t'), 19.80 (t'), 25.50 (t'), 28.46 (t'), 29.25 (t'), 30.75 (t'), 62.23 (t'),

67.37 (t'), 84.37 (s'), 98.78 (d'), 107.42 (s'); exact mass m/z calcd for $C_{15}H_{28}O_2Si$ 268.18585, found 268.18529.

2-(6-Heptynyloxy)tetrahydro-2H-pyran (59).



K_2CO_3 (0.677 g, 4.90 mmol) was added in one portion to a stirred and cooled (0 °C) solution of **58** (1.31 g, 4.89 mmol) in 2:1 MeOH-THF (51 mL). The resulting mixture was stirred for 5 h, the cold bath was removed, and stirring was continued for 12 h. The mixture was then filtered through a pad (2 x 3 cm) of Celite, using Et_2O (50 mL) as a rinse. Evaporation of the combined filtrates, and flash chromatography of the residue over silica gel (2.5 x 20 cm), using 1:10 EtOAc-hexane, gave **59**³³ (0.905 g, 94%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3296, 2117 cm^{-1} ; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.36-1.87 (m, 12 H), 1.91 (t, J = 2.5 Hz, 1 H), 2.17 (td, J = 6.6, 2.5 Hz, 2 H), 3.37 (dt, J = 9.6, 6.2 Hz, 1 H), 3.41-3.55 (m, 1 H), 3.72 (dt, J = 9.6, 6.2 Hz, 1 H), 3.76-3.92 (m, 1 H), 4.54 (dd, J = 3.6, 3.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.38 (t'), 19.68 (t'), 25.46 (t'), 25.52 (t'), 28.34 (t'), 29.26 (t'), 30.78 (t'), 62.33 (t'), 67.38 (t'), 68.21 (d'), 84.53 (s'), 98.86 (d'); exact mass m/z calcd for $C_{12}H_{19}O_2$ (M - 1) 195.13850, found 195.13841.

Trimethyl[8-[(tetrahydro-2H-pyran-2-yl)oxy]-2-octynyl]silane (**60**).



n-BuLi (2.5 M in hexane, 0.40 mL, 1.00 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **59** (0.200 g, 1.00 mmol) in THF (15 mL). Stirring at -78 °C was continued for 20 min, and then Me₃SiCH₂OSO₂CF₃ (0.237 g, 1.00 mmol) was added in one portion, followed immediately by HMPA (0.3 mL), which was also added rapidly in one portion. The cold bath was removed and stirring was continued for 18 h. The resulting mixture was poured into water (25 mL) and extracted with hexane (3 x 25 mL). The combined organic extracts were dried and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 1:20 EtOAc-hexane, gave **60** [0.215 g, 91% after correction for recovered **59** (18%)] as a pure (¹H NMR, 400 MHz), colorless oil: FTIR (CH₂Cl₂ cast) 2940, 2868, 1352 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.07 (s, 9 H), 1.35-1.63 [m, including triplet (2 H) at δ 1.38, *J* = 2.6 Hz, 12 H], 1.64-1.73 (m, 1 H), 1.75-1.86 (m, 1 H), 2.13 (tt, *J* = 6.5, 2.4 Hz, 2 H), 3.36 (dt, *J* = 9.6, 6.8 Hz, 1 H), 3.43-3.51 (m, 1 H), 3.71 (dt, *J* = 9.6, 6.8 Hz, 1 H), 3.80-3.88 (m, 1 H), 4.55 (dd, *J* = 3.6, 3.6 Hz, 1 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ -2.09 (q'), 6.94 (t'), 18.88 (t'), 19.64 (t'), 25.53 (t'), 29.31 (t'), 29.34 (t'), 30.77 (t'),

62.22 (t'), 67.52 (t'), 77.40 (s'), 78.70 (s'), 98.79 (d');
exact mass m/z calcd for $C_{16}H_{30}O_2Si$ 282.20151, found
282.20168.

8-(Trimethylsilyl)-6-octyn-1-ol (61).



TsOH.H₂O (20.0 mg, 0.105 mmol) was added to a stirred solution of **60** (0.860 g, 3.05 mmol) in 3:1 MeOH-H₂O (200 mL), and the mixture was refluxed for 3 h, cooled, and concentrated. The resulting aqueous mixture was extracted with Et₂O (3 x 30 mL), and the combined organic extracts were washed with saturated aqueous NaHCO₃ (20 mL), water (20 mL) and brine (20 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 2:8 EtOAc-hexane, gave **61** (0.560 g, 93%) as a pure (¹H NMR, 200 MHz), colorless oil: FTIR (CH₂Cl₂ cast) 3334 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 0.04 (s, 9 H), 1.28-1.63 [m, including triplet (2 H) at δ 1.36, J = 2.6 Hz, 8 H], 2.01 (br s, 1 H), 2.11 (tt, J = 6.2, 2.2 Hz, 2 H), 3.57 (t, J = 6.4 Hz, 2 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ -2.13 (q'), 6.88 (t'), 18.84 (t'), 24.93 (t'), 29.16 (t'), 32.25 (t'), 62.73 (t'), 77.48 (s'), 78.60 (s'); exact mass m/z calcd for $C_{11}H_{22}OSi$ 198.14400, found 198.14457.

8-(Trimethylsilyl)-6-octynal (38).



DMSO (0.067 mL, 0.9 mmol) was added to a stirred and cooled (-78 °C) solution of (COCl)₂ (0.063 mL, 0.72 mmol) in CH₂Cl₂ (10 mL). Stirring at -78 °C was continued for 20 min, and then a solution of **61** (47.4 mg, 0.24 mmol) in CH₂Cl₂ (2 mL) was added by syringe over 1 min. Stirring was continued for 30 min at -78 °C, and then Et₃N (0.28 mL, 1.98 mmol) was added dropwise over 2 min. The cold bath was removed, and the mixture was stirred for 3 h, diluted with water (1 mL) and CH₂Cl₂ (10 mL), and transferred to a separatory funnel. The organic phase was washed with brine (10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:10 EtOAc-hexane, gave **38** (37.5 mg, 80%) as a pure (¹H NMR, 300 MHz), colorless oil: FTIR (CH₂Cl₂, cast) 2718, 1727 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.07 (s, 9 H), 1.39 (t, *J* = 2.5 Hz, 2 H), 1.48 (tt, *J* = 7.5, 7.5 Hz, 2 H), 1.72 (tt, *J* = 7.5, 7.5 Hz, 2 H), 2.15 (tt, *J* = 7.5, 2.5 Hz, 2 H), 2.42 (td, *J* = 7.5, 1.8 Hz, 2 H), 9.74 (t, *J* = 1.8 Hz, 1 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ -2.10 (q'), 6.91 (t'), 18.66 (t'), 21.23 (t'), 28.74 (t'), 43.37 (t'), 77.92 (s'), 78.00 (s'), 202.35 (d'); exact mass *m/z* calcd for C₁₁H₂₀OSi 196.12834, found 196.12779.

3-Phenyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-1-pentanol (63).



3,4-Dihydro-2H-pyran (2.48 mL, 27.8 mmol) and TsOH.H₂O (30.0 mg, 0.174 mmol) were added to a stirred solution of **62**³⁴ (5.00 g, 27.8 mmol) in Et₂O (300 mL). Stirring was continued for 24 h, and the solution was washed with saturated aqueous NaHCO₃ (50 mL), water (50 mL) and brine (50 mL), dried and evaporated. Flash chromatography of the residue over silica gel (3 x 25 cm), using 3:7 EtOAc-hexane, gave **63** [3.10 g, 66% after correction for recovered diol (36%)] as a colorless oil that was a mixture of two diastereoisomers (¹H NMR, 300 MHz): FTIR (CH₂Cl₂ cast) 3424 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.39-2.09 (m, 11 H), 2.78-2.98 (m, 1 H), 3.09-3.32 (m, 1 H), 3.32-3.70 (m, 4 H), 3.70-3.87 (m, 1 H), 4.41 (dd, *J* = 3.6, 3.6 Hz, 0.5 H), 4.47 (dd, *J* = 3.6, 3.6 Hz, 0.5 H), 7.00-7.38 (m, 5 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 19.44 (t'), 19.68 (t'), 25.35 (t'), 30.60 (t'), 30.69 (t'), 36.48 (t'), 36.50 (t'), 38.88 (d'), 39.18 (d'), 39.47 (t'), 39.64 (t'), 60.70 (t'), 62.03 (t'), 62.42 (t'), 65.63 (t'), 98.63 (d'), 99.19 (d'), 126.20 (d'), 127.57 (d'), 128.39 (d'), 144.46 (s'); exact mass *m/z* calcd for C₁₆H₂₄O₃ 264.17255, found 264.17227.

3-Phenyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]pentyl
4-Methylbenzenesulfonate (64).



Alcohol **63** (3.10 g, 11.7 mmol) was added to a stirred solution of TsCl (3.13 g, 16.4 mmol), pyridine (3.80 mL, 47.0 mmol) and DMAP (0.360 g, 2.94 mmol) in CH_2Cl_2 (200 mL). Stirring was continued for 12 h, and the mixture was quenched with water (50 mL), and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine (40 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (3 x 25 cm), using 3:7 EtOAc-hexane, gave **64** (3.10 g, 63%) as a colorless oil that was a mixture of two diastereoisomers (^1H NMR, 300 MHz): FTIR (CH_2Cl_2 cast) 1362, 1176 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.40-2.00 (m, 9 H), 2.00-2.16 (m, 1 H), 2.44 (s, 3 H), 2.72-2.90 (m, 1 H), 3.02-3.23 (m, 1 H), 3.33-3.47 (m, 1 H), 3.47-3.64 (m, 1 H), 3.64-3.86 (m, 2 H), 3.86-3.99 (m, 1 H), 4.38 (dd, $J = 3.2, 3.2$ Hz, 0.5 H), 4.46 (dd, $J = 3.2, 3.2$ Hz, 0.5 H), 6.96-7.05 (m, 2 H), 7.11-7.27 (m, 3 H), 7.29 (d, $J = 7.9$ Hz, 2 H), 7.71 (d, $J = 7.9$ Hz, 2 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 19.49 (t'), 19.68 (t'), 21.63 (q'), 25.45 (t'), 30.66 (t'), 30.73 (t'), 35.70 (t'), 38.85 (t'), 36.44 (t'), 38.56 (d'), 38.73 (d'), 62.06 (t'), 62.37 (t'), 65.29 (t'), 65.31 (t'), 68.66 (t'), 68.72 (t'), 98.67 (d'), 99.13 (d'), 126.55 (d'), 127.59 (d'), 127.88 (d'), 128.57 (d'), 129.79 (d'), 133.16 (s'), 142.92

(s'), 144.59 (s'); exact mass m/z calcd for $C_{23}H_{30}O_5S$ 418.18140, found 418.18123.

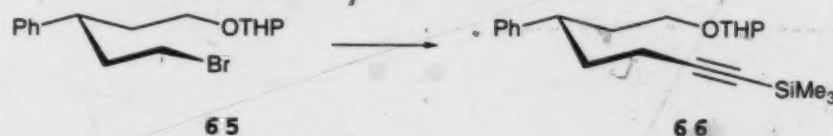
2-[(5-Bromo-3-phenylpentyl)oxy]tetrahydro-2H-pyran (65).



A solution of **64** (2.60 g, 6.22 mmol) and LiBr (5.40 g, 6.23 mmol) in acetone (150 mL) was refluxed for 2 h, cooled and evaporated. The residue was diluted with water (40 mL), and extracted with Et₂O (4 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 x 35 cm), using 2:8 EtOAc-hexane, gave **65** (1.93 g, 95%) as a colorless oil that was a mixture of two diastereoisomers (¹H NMR, 300 MHz): FTIR (CH₂Cl₂ cast) unexceptional; ¹H NMR (CDCl₃, 300 MHz) δ 1.40-1.62 (m, 4 H), 1.62-1.74 (m, 1 H), 1.74-2.06 (m, 3 H), 2.06-2.40 (m, 2 H), 2.89-3.05 (m, 1 H), 3.05-3.35 (m, 3 H), 3.35-3.50 (m, 1 H), 3.54-3.71 (m, 1 H), 3.71-3.87 (m, 1 H), 4.44 (dd, $J = 3.5$, 3.5 Hz, 0.5 H), 4.50 (dd, $J = 3.5$, 3.5 Hz, 0.5 H), 7.10-7.40 (m, 5 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 19.49 (t'), 19.66 (t'), 25.46 (t'), 25.48 (t'), 30.68 (t'), 30.74 (t'), 31.83 (t'), 36.25 (t'), 36.31 (t'), 39.67 (t'), 39.76 (t'), 41.03 (d'), 41.16 (d'), 62.06 (t'), 62.34 (t'), 65.42 (t'), 65.44 (t'), 98.66 (d'), 99.12 (d'), 126.61 (d'), 127.71 (d'), 128.62

(d'), 143.08 (s'), 143.13 (s'); exact mass m/z calcd for $C_{16}H_{23}^{81}BrO_2$ 328.08609, found 328.08641.

Trimethyl[5-phenyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-1-heptynyl]silane (66).



n -BuLi (2.5 M in hexane, 1.13 mL, 2.83 mmol) was added to a stirred and cooled ($-78\text{ }^{\circ}\text{C}$) solution of trimethylsilylacetylene (0.43 mL, 2.83 mmol) in THF (10 mL). Stirring at $-78\text{ }^{\circ}\text{C}$ was continued for 1.5 h, and then **65** (0.396 g, 1.21 mmol) and HMPA (0.5 mL, 2.9 mmol) were added rapidly, each in one portion. The cold bath was removed and stirring was continued for 10 h. The mixture was quenched with water (5 mL) at $-78\text{ }^{\circ}\text{C}$, and extracted with hexane (3 x 10 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 1:10 EtOAc-hexane, gave **66** (0.377 g, 81%) as a colorless oil that was a mixture of two diastereoisomers (^1H NMR, 300 MHz): FTIR (CH_2Cl_2 cast) 2174 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.17 (s, 9 H), 1.37-2.15 (m, 12 H), 2.76-2.94 (m, 1 H), 3.10-3.27 (m, 1 H), 3.34-3.48 (m, 1 H), 3.52-3.69 (m, 1 H), 3.69-3.85 (m, 1 H), 4.43 (dd, $J = 3.4, 3.4\text{ Hz}$, 0.5 H), 4.49 (dd, $J = 3.4, 3.4\text{ Hz}$, 0.5 H), 7.10-7.30 (m, 5 H); ^{13}C NMR

(CDCl₃, 75.5 MHz) δ 0.16 (q'), 17.97 (t'), 19.45 (t'), 19.64 (t'), 25.47 (t'), 30.69 (t'), 30.74 (t'), 35.65 (t'), 35.75 (t'), 36.29 (t'), 36.35 (t'), 41.51 (d'), 41.64 (d'), 61.96 (t'), 62.25 (t'), 65.60 (t'), 84.62 (s'), 98.54 (d'), 99.05 (d'), 107.19 (s'), 126.29 (d'), 127.72 (d'), 128.39 (d'), 143.90 (s'); exact mass m/z calcd for C₂₁H₃₂O₂Si 344.21716, found 344.21734.

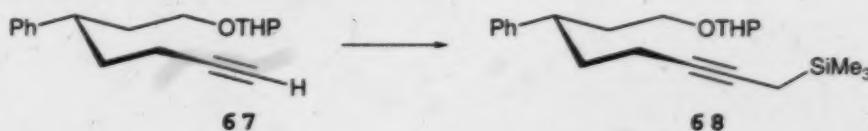
2-[(3-Phenyl-6-heptynyl)oxy]tetrahydro-2H-pyran (67).



K₂CO₃ (0.154 g, 1.11 mmol) was added in one portion to a stirred and cooled (0 °C) solution of **66** (0.381 g, 1.11 mmol) in 2:1 MeOH-THF (15 mL), and stirring at 0 °C was continued for 6 h. The cold bath was removed, stirring was continued for 12 h, and the mixture was then filtered through a pad (1 x 2 cm) of Celite, using Et₂O (20 mL) as a rinse. Evaporation of the combined filtrates, and flash chromatography of the residue over silica gel (1.5 x 15 cm), using 1:10 EtOAc-hexane, gave **67** (0.284 g, 94%) as a colorless oil that was a mixture of two diastereoisomers (¹H NMR, 300 MHz): FTIR (CH₂Cl₂ cast) 3296, 2116 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.45-2.16 (m, 13 H), 2.82-2.96 (m, 1 H), 3.18-3.32 (m, 1 H), 3.41-3.52 (m, 1 H), 3.60-3.74 (m, 1 H),

3.74-3.90 (m, 1 H), 4.47 (dd, $J = 3.3, 3.3$ Hz, 0.5 H), 4.53 (dd, $J = 3.3, 3.3$ Hz, 0.5 H), 7.12-7.41 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 16.46 (t'), 16.49 (t'), 19.45 (t'), 19.59 (t'), 25.43 (t'), 30.64 (t'), 30.70 (t'), 35.48 (t'), 35.62 (t'), 36.29 (t'), 36.35 (t'), 41.42 (d'), 41.56 (d'), 61.97 (t'), 62.21 (t'), 65.55 (t'), 65.59 (t'), 68.39 (d'), 68.42 (d'), 84.20 (s'), 98.56 (d'), 98.98 (d'), 126.31 (d'), 127.66 (d'), 128.41 (d'), 143.80 (s'), 143.85 (s'); exact mass m/z calcd for $\text{C}_{18}\text{H}_{24}\text{O}_2$ 272.17764, found 272.17726.

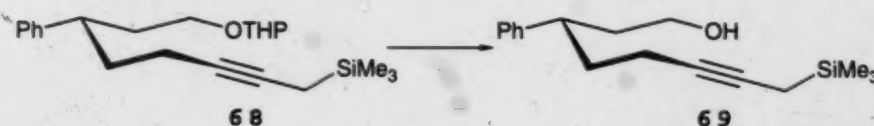
Trimethyl[6-phenyl-8-[(tetrahydro-2H-pyran-2-yl)oxy]-2-octynyl]silane (68).



$n\text{-BuLi}$ (2.5 M in hexane, 1.20 mL, 3.00 mmol) was added to a stirred and cooled (-78°C) solution of **67** (0.652 g, 2.40 mmol) in THF (15 mL). Stirring at -78°C was continued for 1.5 h, and then $\text{Me}_3\text{SiCH}_2\text{OSO}_2\text{CF}_3$ (0.60 mL, 3.00 mmol) and HMPA (0.5 mL) were added rapidly, each in one portion. The cold bath was removed and stirring was continued for 10 h. The mixture was poured into water (25 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 1:10 EtOAc-hexane, gave **68** (0.791 g, 92%) as a colorless oil that was a mixture of two

diastereoisomers (^1H NMR, 300 MHz): FTIR (CH_2Cl_2 cast) unexceptional; ^1H NMR (CDCl_3 , 300 MHz) δ 0.10 (s, 9 H), 1.38-2.11 (m, 14 H), 2.76-2.94 (m, 1 H), 3.11-3.26 (m, 1 H), 3.35-3.48 (m, 1 H), 3.53-3.69 (m, 1 H), 3.70-3.86 (m, 1 H), 4.43 (dd, $J = 3.4, 3.4$ Hz, 0.5 H), 4.49 (dd, $J = 3.4, 3.4$ Hz, 0.5 H), 7.03-7.37 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ -2.00 (q'), 7.00 (t'), 17.05 (t'), 19.50 (t'), 19.68 (t'), 25.51 (t'), 30.71 (t'), 30.77 (t'), 36.33 (t'), 36.38 (t'), 36.65 (t'), 36.77 (t'), 41.54 (d'), 41.68 (d'), 62.00 (t'), 62.28 (t'), 65.80 (t'), 77.48 (t'), 77.57 (s'), 78.43 (s'), 78.47 (s'), 98.61 (d'), 99.06 (d'), 126.19 (d'), 127.15 (d'), 128.36 (d'), 144.31 (s'), 144.36 (s'); exact mass m/z calcd for $\text{C}_{22}\text{H}_{34}\text{O}_2\text{Si}$ 358.23282, found 358.23321.

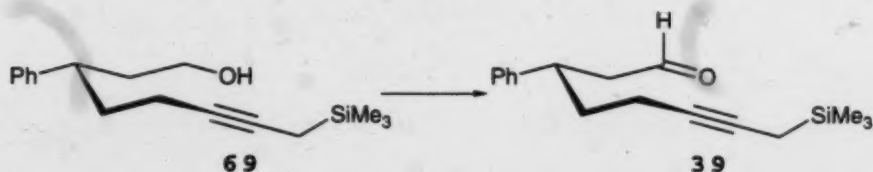
3-Phenyl-8-(trimethylsilyl)-6-octyn-1-ol (69).



$\text{TsOH} \cdot \text{H}_2\text{O}$ (30.0 mg, 0.158 mmol) was added to a stirred solution of **68** (0.685 g, 1.91 mmol) in 3:1 MeOH- H_2O (150 mL), and the mixture was refluxed for 4 h, cooled, and concentrated. The resulting aqueous mixture was extracted with Et_2O (3 x 20 mL), and the combined organic extracts were washed with saturated aqueous NaHCO_3 (20 mL), water (20 mL), and brine (20 mL); dried, and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm),

using 2:8 EtOAc-hexane, gave **69** (0.469 g, 89%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3332 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.10 (s, 9-H), 1.16 (t, $J = 5.0\text{ Hz}$, 1 H), 1.43 (t, $J = 2.3\text{ Hz}$, 2 H), 1.65-2.12 (m, 6 H), 2.87 (dddd, $J = 4.7, 4.7, 4.7, 4.7\text{ Hz}$, 1 H), 3.40-3.60 (m, 2 H), 7.12-7.34 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ -2.01 (q'), 6.99 (t'), 17.03 (t'), 36.60 (t'), 39.27 (t'), 41.39 (d'), 61.18 (t'), 77.79 (s'), 78.34 (s'), 126.38 (d'), 127.68 (d'), 128.53 (d'), 144.20 (s'); exact mass m/z calcd for $\text{C}_{17}\text{H}_{26}\text{OSi}$ 274.17529, found 274.17522.

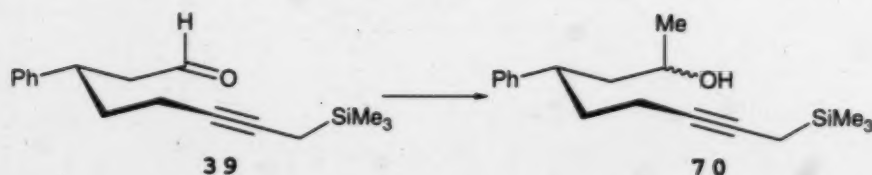
3-Phenyl-8-(trimethylsilyl)-6-octynal (39).



DMSO (0.19 mL, 2.67 mmol) was added to a stirred and cooled ($-78\text{ }^{\circ}\text{C}$) solution of $(\text{COCl})_2$ (0.19 mL, 2.18 mmol) in CH_2Cl_2 (25 mL). Stirring at $-78\text{ }^{\circ}\text{C}$ was continued for 20 min, and then a solution of **69** (0.147 g, 0.536 mmol) in CH_2Cl_2 (2 mL) was added by syringe over 1 min. Stirring was continued for 30 min at $-78\text{ }^{\circ}\text{C}$, and then Et_3N (0.76 mL, 5.45 mmol) was added. The cold bath was removed, and the mixture was stirred for 3 h, diluted with water (1 mL) and CH_2Cl_2 (10 mL), and transferred to a separatory funnel. The organic phase was washed with brine (10 mL), dried, and evaporated. Flash

chromatography of the residue over silica gel (2 x 15 cm), using (1:10 EtOAc-hexane, gave **39** (0.132 g, 90%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1725 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.12 (s, 9 H), 1.43 (t, $J = 2.4$ Hz, 2 H), 1.67-2.15 (m, 4 H), 2.63-2.81 (m, 2 H), 3.30-3.43 (m, 1 H), 7.15-7.37 (m, 5 H), 9.66 (t, $J = 1.8$ Hz, 1 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ -1.97 (q'), 7.03 (t'), 16.90 (t'), 36.18 (t'), 38.98 (d'), 50.08 (t'), 77.70 (s'), 78.36 (s'), 126.83 (d'), 127.59 (d'), 128.75 (d'), 142.97 (s'), 201.69 (d'); exact mass m/z calcd for $\text{C}_{17}\text{H}_{24}\text{OSi}$ 272.15964, found 272.15907.

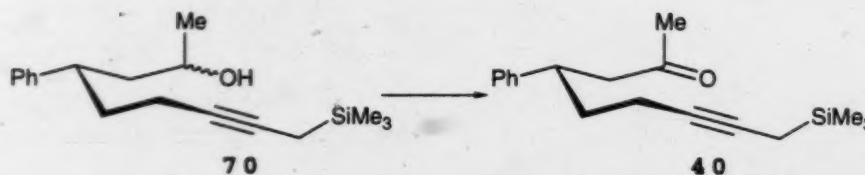
4-Phenyl-9-(trimethylsilyl)-7-nonyn-2-ol (70).



A solution of **39** (46.6 mg, 0.171 mmol) in Et_2O (3 mL) was added dropwise to a stirred and cooled ($0\text{ }^\circ\text{C}$) solution of MeMgBr (0.36 mmol) in Et_2O (15 mL). The cold bath was removed and stirring was continued for 2 h. The mixture was quenched with saturated aqueous NH_4Cl solution (5 mL) at $0\text{ }^\circ\text{C}$ and extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with brine (10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 2:8 EtOAc-hexane, gave **70** (44.6 mg,

90%) as a pure (^1H NMR, 400 MHz), colorless oil, which was a 1:1 mixture of diastereoisomers (^1H NMR, 400 MHz): FTIR (CH_2Cl_2 cast) 3347 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 0.10 (s, 9 H), 1.12 (d, $J = 5.9\text{ Hz}$, 3 H), 1.39 (br s, 1 H), 1.43 (t, $J = 2.5\text{ Hz}$, 2 H), 1.64–2.08 (m, 6 H), 2.97 (dddd, $J = 4.9, 4.9, 4.9, 4.9\text{ Hz}$, 1 H), 3.43–3.56 (m, 1 H), 7.15–7.33 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ -2.01 (q'), 7.00 (t'), 16.90 (t'), 17.09 (t'), 23.24 (q'), 24.25 (q'), 36.70 (t'), 37.01 (t'), 41.37 (d'), 41.98 (d'), 45.98 (t'), 46.05 (t'), 65.65 (d'), 66.55 (d'), 77.70 (s'), 77.81 (s'), 78.31 (s'), 78.43 (s'), 126.29 (d'), 126.44 (d'), 127.64 (d'), 127.84 (d'), 128.50 (d'), 128.61 (d'), 144.33 (s'), 144.37 (s'); exact mass m/z calcd for $\text{C}_{18}\text{H}_{28}\text{OSi}$ 288.19095, found 288.19067.

4-Phenyl-9-(trimethylsilyl)-7-nonyn-2-one (40).



A solution of alcohols **70** (0.140 g, 0.486 mmol) in CH_2Cl_2 (4 mL) was added to a stirred mixture of PCC (1.63 g, 7.56 mmol) and powdered molecular sieves (3Å, 3.1 g) in CH_2Cl_2 (20 mL). The mixture was stirred for 25 min, diluted with Et_2O (20 mL), and filtered through a pad (2 x 2 cm) of flash chromatography silica gel, using Et_2O (30 mL) as a rinse. Evaporation of the combined filtrates, and flash

chromatography of the residue over silica gel (1 x 15 cm), using 1:10 EtOAc-hexane, gave **40** (0.126 g, 90%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1717 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.10 (s, 9 H), 1.42 (t, $J = 2.4\text{ Hz}$, 2 H), 1.61-2.10 [m, including singlet at δ 2.01 (3 H), 7 H], 2.71 (dd, $J = 16.5, 7.6\text{ Hz}$, 1 H), 2.76 (dd, $J = 16.5, 7.6\text{ Hz}$, 1 H), 3.22-3.35 (m, 1 H), 7.10-7.33 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ -2.03 (q'), 6.99 (t'), 16.98 (t'), 30.44 (d'), 36.11 (t'), 40.31 (d'), 50.49 (t'), 77.93 (s'), 77.99 (s'), 126.56 (d'), 127.55 (d'), 128.54 (d'), 143.52 (s'), 207.46 (s'); exact mass m/z calcd for $\text{C}_{18}\text{H}_{26}\text{OSi}$ 286.17529, found 286.17498.

3-Phenyl-5-[(tetrahydro-2H-pyran-2-yl)oxyl]pentanal (71).



A solution of **63** (0.154 g, 0.583 mmol) in CH_2Cl_2 (4 mL) was added to a stirred mixture of PCC (1.32 g, 6.12 mmol) and powdered molecular sieves (3Å, 1.90 g) in CH_2Cl_2 (25 mL). The mixture was stirred for 35 min, diluted with Et_2O (20 mL), and filtered through a pad (2 x 2 cm) of flash chromatography silica gel, using Et_2O (30 mL) as a rinse. Evaporation of the combined filtrates, and flash chromatography of the residue over silica gel (1 x 15 cm), using 1:10 EtOAc-hexane, gave **71** (0.125 g, 82%) as a colorless oil that was a mixture

of two diastereoisomers (^1H NMR, 300 MHz): FTIR (CH_2Cl_2 cast) 2723, 1724 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.42–2.07 (m, 8 H), 2.75 (dd, $J = 7.4, 1.9$ Hz, 2 H), 3.11–3.22 (m, 1 H), 3.32–3.53 (m, 2 H), 3.55–3.86 (m, 2 H), 4.43 (dd, $J = 3.6, 3.6$ Hz, 0.5 H), 4.49 (dd, $J = 3.6, 3.6$ Hz, 0.5 H), 7.10–7.30 (m, 5 H), 9.66 (t, $J = 1.9$ Hz, 1 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 19.38 (t'), 19.59 (t'), 25.34 (t'), 30.56 (t'), 30.63 (t'), 36.23 (t'), 36.29 (t'), 36.80 (d'), 36.92 (d'), 50.18 (t'), 50.32 (t'), 61.97 (t'), 62.29 (t'), 64.91 (t'), 64.98 (t'), 98.53 (d'), 99.06 (d'), 126.60 (d'), 127.43 (d'), 128.57 (d'), 143.16 (s'), 143.22 (s'), 201.54 (d'), 201.57 (d'); exact mass m/z calcd for $\text{C}_{16}\text{H}_{22}\text{O}_3$ 262.15689, found 262.15621.

2-[(6,6-Dibromo-3-phenyl-5-hexenyl)oxy]tetrahydro-2H-pyran (72).



A solution of CBr_4 (2.78 g, 8.40 mmol) in CH_2Cl_2 (75 mL) was added at a fast dropwise rate to a stirred and cooled (-20 $^{\circ}\text{C}$) solution of Ph_3P (2.20 g, 8.40 mmol) in CH_2Cl_2 (75 mL). Stirring at -20 $^{\circ}\text{C}$ was continued for 15 min, and then a solution of **71** (1.10 g, 4.20 mmol) and Et_3N (0.59 mL, 4.20 mmol) in CH_2Cl_2 (40 mL) was added dropwise at -60 $^{\circ}\text{C}$. The cold bath was removed, stirring was continued for 30 min, and the mixture was filtered through a pad (2 x 3 cm) of flash

chromatography silica gel, using Et₂O (50 mL) as a rinse. Evaporation of the combined filtrates, and flash chromatography of the residue over silica gel (1.5 x 25 cm), using 1:20 EtOAc-hexane, gave **72** (1.34 g, 76%) as a colorless oil that was a mixture of two diastereoisomers (¹H NMR, 300 MHz): FTIR (CH₂Cl₂ cast) unexceptional; ¹H NMR (CDCl₃, 300 MHz) δ 1.42-2.10 (m, 8 H), 2.30-2.57 (m, 2 H), 2.82-2.97 (m, 1 H), 3.11-3.31 (m, 1 H), 3.36-3.50 (m, 1 H), 3.53-3.86 (m, 2 H), 4.42 (dd, *J* = 3.2, 3.2 Hz, 0.5 H), 4.49 (dd, *J* = 3.2, 32.2 Hz, 0.5 H), 6.26 (t, *J* = 7.1 Hz, 1 H), 7.10-7.36 (m, 5 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 19.49 (t'), 19.68 (t'), 25.43 (t'), 30.66 (t'), 30.71 (t'), 35.69 (t'), 35.77 (t'), 40.05 (t'), 40.14 (t'), 41.29 (d'), 41.47 (d'), 62.05 (t'), 62.37 (t'), 65.30 (t'), 65.34 (t'), 89.40 (s'), 89.46 (s'), 98.66 (d'), 99.14 (d'), 126.57 (d'), 126.70 (d'), 127.51 (d'), 128.53 (d'), 128.64 (d'), 136.88 (d'), 136.93 (d'), 143.42 (s'), 143.47 (s'); exact mass *m/z* calcd for C₁₇H₂₂⁸¹Br₂O₂ 419.99457, found 419.99404.

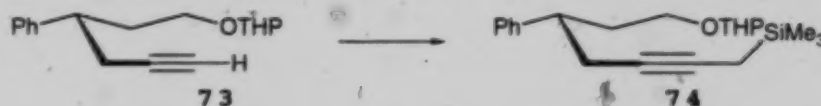
2-[(3-Phenyl-5-hexynyl)oxy]tetrahydro-2H-pyran
(**73**).



n-BuLi (2.5 M in hexane, 0.88 mL, 2.20 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **72**

(0.440 g, 1.05 mmol) in THF (30 mL). Stirring at -78°C was continued for 2 h, and then water (1.0 mL) was added. The cold bath was removed, stirring was continued for 30 min, and the mixture was diluted with Et_2O (20 mL) and washed with brine (20 mL). The organic extract was dried and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 1:20 EtOAc -hexane, gave **73** (0.255 g, 94%) as a colorless oil that was a mixture of two diastereoisomers (^1H NMR, 300 MHz): FTIR (CH_2Cl_2 cast) 3290, 2117 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.40-2.03 (m, 8 H), 2.14-2.27 (m, 1 H), 2.46-2.56 (m, 2 H), 2.92-3.08 (m, 1 H), 3.16-3.34 (m, 1 H), 3.35-3.48 (m, 1 H), 3.57-3.86 (m, 2 H), 4.44 (dd, $J = 3.3$, 3.3 Hz, 0.5 H), 4.53 (dd, $J = 3.3$, 3.3 Hz, 0.5 H), 7.13-7.38 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 19.36 (t'), 19.55 (t'), 25.39 (t'), 26.07 (t'), 26.27 (t'), 3.57 (t'), 30.64 (t'), 34.69 (t'), 34.76 (t'), 41.17 (d'), 41.37 (d'), 61.84 (t'), 62.18 (t'), 65.21 (t'), 65.30 (t'), 69.76 (d'), 82.57 (s'), 98.40 (d'), 98.93 (d'), 126.52 (d'), 127.45 (d'), 128.28 (d'), 128.40 (d'), 143.46 (s'); exact mass m/z calcd for $\text{C}_{17}\text{H}_{22}\text{O}_2$ 258.16199, found 258.16187.

Trimethyl[5-phenyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-2-heptynyl]silane (74).



$n\text{-BuLi}$ (2.5 M in hexane, 0.50 mL, 1.25 mmol) was added

dropwise to a stirred and cooled (-78°C) solution of **73** (0.255 g, 0.988 mmol) in THF (18 mL). Stirring at -78°C was continued for 1 h, and then $\text{Me}_3\text{SiCH}_2\text{OSO}_2\text{CF}_3$ (0.25 mL, 1.25 mmol) and HMPA (0.50 mL, 2.88 mmol) were added rapidly, each in one portion. The cold bath was removed and stirring was continued for 10 h. The mixture was diluted with Et_2O (20 mL) and washed with brine (20 mL). The aqueous phase was extracted with Et_2O (2 x 20 mL) and the combined organic extracts were dried and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 1:20 EtOAc -hexane, gave **74** (0.292 g, 86%) as a colorless oil that was a mixture of two diastereoisomers (^1H NMR, 300 MHz): FTIR (CH_2Cl_2 cast) unexceptional; ^1H NMR (CDCl_3 , 300 MHz) δ 0.03 (s, 9 H), 1.38 (t, $J = 2.6$ Hz, 2 H), 1.43-1.97 (m, 7 H), 2.12-2.26 (m, 1 H), 2.42-2.52 (m, 2 H), 2.84-2.98 (m, 1 H), 3.15-3.32 (m, 1 H), 3.35-3.48 (m, 1 H), 3.56-3.86 (m, 2 H), 4.45 (dd, $J = 3.4, 3.4$ Hz, 0.5 H), 4.52 (dd, $J = 3.4, 3.4$ Hz, 0.5 H), 7.14-7.34 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ -2.10 (q'), 7.00 (t'), 19.41 (t'), 19.58 (t'), 25.51 (t'), 26.67 (t'), 26.85 (t'), 30.68 (t'), 30.74 (t'), 35.08 (t'), 35.10 (t'), 42.10 (d'), 42.33 (d'), 61.89 (t'), 62.19 (t'), 65.53 (t'), 65.56 (t'), 76.88 (s'), 78.91 (s'), 98.47 (d'), 98.94 (d'), 126.30 (d'), 126.47 (d'), 127.49 (d'), 127.69 (d'), 128.26 (d'), 128.42 (d'), 144.30 (s'); exact mass m/z calcd for $\text{C}_{21}\text{H}_{32}\text{O}_2\text{Si}$ 344.21716, found 344.21696.

3-Phenyl-7-(trimethylsilyl)-5-heptyn-1-ol (75).



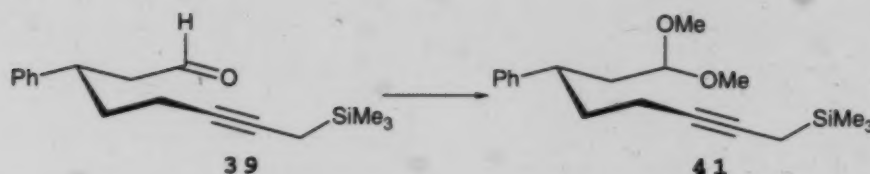
TsOH·H₂O (12.0 mg, 0.063 mmol) was added to a stirred solution of **74** (0.292 g, 0.848 mmol) in 3:1 MeOH-H₂O (80 mL), and the mixture was refluxed for 3.5 h, cooled, and concentrated. The resulting aqueous mixture was extracted with Et₂O (3 x 20 mL). The combined organic extracts were washed with saturated aqueous NaHCO₃ (20 mL), water (20 mL) and brine (20 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 2:8 EtOAc-hexane, gave **75** (0.216 g, 98%) as a pure (¹H NMR, 300 MHz), colorless oil: FTIR (CH₂Cl₂ cast) 3332 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.04 (s, 9 H), 1.38 (t, *J* = 2.6 Hz, 2 H), 1.47 (br s, 1 H), 1.79-1.93 (m, 1 H), 2.05-2.19 (m, 1 H), 2.38-2.57 (m, 2 H), 2.83-2.96 (m, 1 H), 3.44-3.64 (m, 2 H), 7.13-7.35 (m, 5 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ -2.07 (q'), 7.00 (t'), 26.72 (t'), 38.09 (t'), 42.08 (d'), 61.05 (t'), 76.81 (s'), 79.12 (s'), 126.50 (d'), 127.49 (d'), 128.44 (d'), 144.22 (s'); exact mass *m/z* calcd for C₁₆H₂₄OSi 260.15964, found 260.15939.

3-Phenyl-7-(trimethylsilyl)-5-heptynal (42).



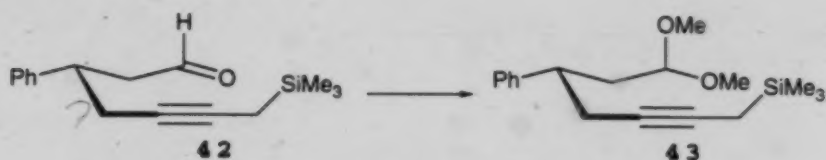
A solution of **75** (0.165 g, 0.635 mmol) in CH_2Cl_2 (5 mL) was added to a stirred mixture of PCC (1.43 g, 6.63 mmol) and powdered molecular sieves (3Å, 2.20 g) in CH_2Cl_2 (30 mL). The mixture was stirred for 30 min, diluted with Et_2O (20 mL), and filtered through a pad (2 x 2 cm) of flash chromatography silica gel, using Et_2O (30 mL) as a rinse. Evaporation of the combined filtrates, and flash chromatography of the residue over silica gel (1 x 15 cm), using 1:10 EtOAc-hexane, gave **42** (0.148 g, 90%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 2722, 2220, 1724 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.06 (s, 9 H), 1.42 (t, $J = 2.7$ Hz, 2 H), 2.47 (ddt, $J = 16.6, 6.0, 2.7$ Hz, 1 H), 2.56 (ddt, $J = 16.6, 5.8, 2.7$ Hz, 1 H), 2.77 (ddd, $J = 17.2, 8.2, 1.8$ Hz, 1 H), 3.02 (ddd, $J = 17.2, 6.2, 1.8$ Hz, 1 H), 3.39 (br dddd, $J = 8.2, 6.2, 6.0, 5.8$ Hz, 1 H), 7.16-7.37 (m, 5 H), 9.72 (t, $J = 1.8$ Hz, 1 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ -2.03 (q'), 7.00 (t'), 26.61 (t'), 39.57 (d'), 48.79 (t'), 75.94 (s'), 80.30 (s'), 126.89 (d'), 127.32 (d'), 128.63 (d'), 143.07 (s'), 201.48 (d'); exact mass m/z calcd for $\text{C}_{16}\text{H}_{21}\text{OSi}$ (M - H) 257.13617, found 257.13608.

(8,8-Dimethoxy-6-phenyl-2-octynyl)trimethylsilane
(41).



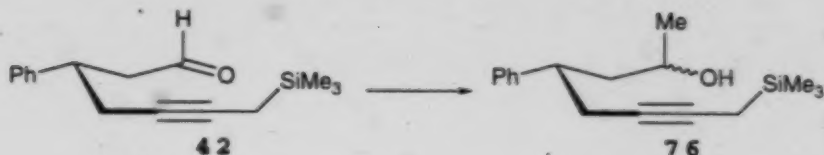
YbCl₃·6H₂O (0.560 g, 1.45 mmol) and CH(OMe)₃ (2.62 mL, 23.9 mmol) were added to a stirred solution of **39** (0.178 g, 0.654 mmol) in MeOH (1.5 mL). Stirring was continued for 10 h, and the mixture was diluted with Et₂O (5 mL) and filtered through a pad (2 x 2 cm) of flash chromatography silica gel, using Et₂O (20 mL) as a rinse. Evaporation of the combined filtrates, and flash chromatography of the residue over silica gel (1.5 x 15 cm), using 1:10 EtOAc-hexane, gave **41** (0.160 g, 77%) as a pure (¹H NMR, 300 MHz), colorless oil: FTIR (CH₂Cl₂ cast) unexceptional; ¹H NMR (CDCl₃, 300 MHz) δ 0.12 (s, 9 H), 1.42 (t, *J* = 2.5 Hz, 2 H), 1.64–2.09 (m, 6 H), 2.86 (dddd, *J* = 4.9, 4.9, 4.9, 4.9 Hz, 1 H), 3.22 (s, 3 H), 3.27 (s, 3 H), 4.07 (dd, *J* = 7.6, 3.7 Hz, 1 H), 7.13–7.36 (m, 5 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ -2.01 (q'), 7.01 (t'), 17.00 (t'), 36.61 (t'), 39.25 (t'), 40.63 (d'), 52.59 (q'), 52.65 (q'), 77.73 (s'), 78.27 (s'), 102.83 (d'), 126.33 (d'), 127.74 (d'), 128.48 (d'), 144.14 (s'); exact mass *m/z* calcd for C₁₉H₃₀O₂Si 318.20151, found 318.20148.

(7,7-Dimethoxy-5-phenyl-2-heptynyl)trimethylsilane (**43**).



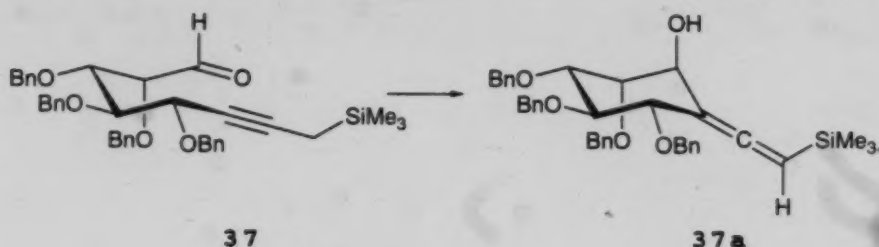
$\text{YbCl}_3 \cdot 6\text{H}_2\text{O}$ (0.30 g, 0.77 mmol) and $\text{CH}(\text{OMe})_3$ (1.60 mL, 14.6 mmol) was added to a stirred solution of **42** (0.102 g, 0.395 mmol) in MeOH (1 mL). Stirring was continued for 10 h, and the mixture was diluted with Et_2O (5 mL) and filtered through a pad (2 x 2 cm) of flash chromatography silica gel, using Et_2O (20 mL) as a rinse. Evaporation of the combined filtrates, and flash chromatography of the residue over silica gel (1.5 x 15 cm), using 1:20 EtOAc-hexane, gave **43** (0.103 g, 86%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) unexceptional; ^1H NMR (CDCl_3 , 300 MHz) δ 0.03 (s, 9 H), 1.38 (t, $J = 2.6$ Hz, 2 H), 1.85 (ddd, $J = 14.3, 9.8, 3.8$ Hz, 1 H), 2.22 (ddd, $J = 14.3, 7.8, 4.8$ Hz, 1 H), 2.37–2.55 (m, 2 H), 2.82–2.94 (m, 1 H), 3.22 (s, 3 H), 3.28 (s, 3 H), 4.15 (dd, $J = 7.8, 3.8$ Hz, 1 H), 7.15–7.34 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ -2.08 (q'), 7.01 (t'), 26.74 (t'), 37.73 (t'), 41.22 (d'), 52.42 (q'), 52.48 (q'), 76.59 (s'), 79.12 (s'), 102.64 (d'), 126.46 (d'), 127.54 (d'), 128.39 (d'), 144.13 (s'); exact mass m/z calcd for $\text{C}_{17}\text{H}_{25}\text{O}_2\text{Si}$ (M - CH_3) 289.16238, found 289.16295.

4-Phenyl-8-(trimethylsilyl)-6-octyn-2-ol (76).



A solution of **42** (120 mg, 0.465 mmol) in Et₂O (5 mL) was added dropwise to a stirred and cooled (0 °C) solution of commercial MeMgBr (3.0 M in Et₂O, 0.31 mL, 0.93 mmol) in Et₂O (35 mL). The cold bath was removed, and stirring was continued for 2 h. The mixture was then recooled to 0 °C, quenched with saturated aqueous NH₄Cl (15 mL), and extracted with Et₂O (3 x 25 mL). The combined organic extracts were washed with brine (20 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 2:8 EtOAc-hexane, gave **76** (115 mg, 90%) as a colorless oil that was a 1:1 mixture of two diastereoisomers (¹H NMR, 300 MHz): FTIR (CH₂Cl₂ cast) 3356 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.04 (s, 9 H), 1.12 (d, *J* = 6.1 Hz, 1.5 H), 1.17 (d, *J* = 6.1 Hz, 1.5 H), 1.39 (dd, *J* = 2.6, 2.6 Hz, 1 H), 1.40 (dd, *J* = 2.6, 2.6 Hz, 1 H), 1.60–2.04 (m, 3 H), 2.33–2.56 (m, 2 H), 2.78–2.92 (m, 0.5 H), 2.94–3.08 (m, 0.5 H), 3.45–3.60 (m, 0.5 H), 3.67–3.82 (m, 0.5 H), 7.14–7.36 (m, 5 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ -2.07 (q'), 6.98 (t'), 23.36 (q'), 24.35 (q'), 26.69 (t'), 27.18 (t'), 42.02 (d'), 42.53 (d'), 44.71 (t'), 44.74 (t'), 65.63 (d'), 66.37 (d'), 76.78 (s'), 76.94 (s'), 79.01 (s'), 79.18 (s'), 126.40 (d'), 126.50 (d'), 127.40 (d'), 127.64 (d'), 128.38 (d'), 128.49 (d'), 144.27

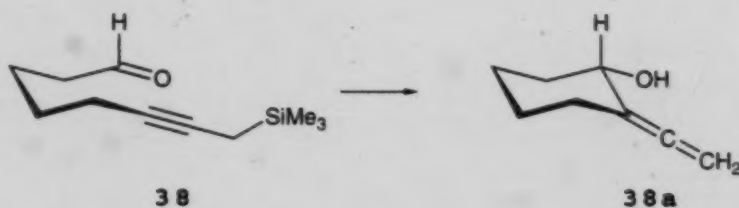
(*R*_a)-5-Deoxy-1,2,3,4-tetrakis-*O*-(phenylmethyl)-5-
 [(trimethylsilyl)ethenylidene]-*L*-chiro-inositol (**37a**).



CSA (6.0 mg, 0.026 mmol) was added to a stirred solution of **37** (96.9 mg, 0.156 mmol) in PhMe (20 mL). Stirring was continued for 5 h, Et₃N (1 mL) was added, and the solution was evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 1:9 EtOAc-hexane, gave **37a** (70.8 mg, 73%) as a pure (¹H NMR, 360 MHz), white solid: FTIR (CH₂Cl₂ cast) 3386, 1948 cm⁻¹; ¹H NMR (CDCl₃, 360 MHz) δ 0.08 (s, 9 H), 1.86 (br s, 1 H), 3.75 (dd, *J* = 6.8, 3.0 Hz, 1 H), 3.89 (dd, *J* = 6.2, 3.0 Hz, 1 H), 3.99 (dd, *J* = 5.8, 5.8 Hz, 1 H), 4.23 (dd, *J* = 5.5, 2.6 Hz, 1 H), 4.48-4.72 (m, 8 H), 4.78 (d, *J* = 11.6 Hz, 1 H), 5.33 (dd, *J* = 2.8, 2.8 Hz, 1 H), 7.20-7.40 (m, 20 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ -0.82 (q'), 68.32 (d'), 71.63 (t'), 72.30 (t'), 72.60 (t'), 73.84 (t'), 77.55 (d'), 78.36 (d'), 79.35 (d'), 79.56 (d'), 86.59 (d'), 95.40 (s'), 127.36 (d'), 127.45 (d'), 127.59 (d'), 127.68 (d'), 127.89 (d'), 128.25 (d'), 128.33 (d'), 128.36 (d'), 138.56 (s'), 138.60 (s'), 138.650 (s'), 138.70 (s'), 206.47 (s'); mass (HR electrospray) *m/z* calcd for C₃₉H₄₄NaO₅Si (*M* + Na) 643.285573, found 643.286700. Crystal data:

Compound **37a** crystallizes in the monoclinic space group $P2_1$ (No. 4) with $a = 11.401$ (2) Å, $b = 12.219$ (2) Å, $c = 13.716$ (2) Å, $\beta = 108.353$ (10)°, $V = 1813.6$ (5) Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.137$ g cm⁻³, $\mu = 0.105$ mm⁻¹. X-ray diffraction data were collected on a Siemens P4/RA instrument with Mo K α radiation ($\lambda = 0.71073$ Å) at -60 °C. The final model, with 6315 unique data used and 407 parameters varied, converged to values of R_1 (F_o) = 0.0810 (for 3100 data with $F_o^2 > 2\sigma(F_o^2)$) and wR_2 (F_o^2) = 0.2366 (all data). The absolute stereochemistry of the molecule was not established from the structural results alone, but was assigned based on the known stereochemistry of its chemical precursors.

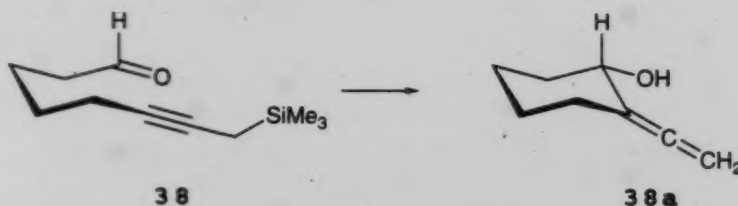
2-Ethenylidenecyclohexanol (38a).⁶⁴ (a) Use of ZnCl_2 .



A solution of **38** (40.0 mg, 0.204 mmol) in CH_2Cl_2 (10 mL) was added to a stirred and cooled (0 °C) suspension of ZnCl_2 (61.0 mg, 0.45 mmol) in CH_2Cl_2 (20 mL). Stirring was continued for 2.5 h, and water (10 mL) was then added. After 2 min, the organic phase was washed with saturated aqueous NaHCO_3 (10 mL), water (10 mL) and brine (10 mL), dried (MgSO_4) and evaporated. Flash chromatography of the residue over

silica gel (1.5 x 15 cm), using 2:8 EtOAc-hexane, gave **38a** (16.7 mg, 66%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3381, 1961 cm^{-1} ; ^1H NMR (CD_2Cl_2 , 300 MHz) δ 1.28-1.46 (m, 3 H), 1.58-1.72 (m, 1 H), 1.72-1.84 [m, 2 H, including doublet at δ 1.79 ($J = 4.5$ Hz, 1 H) which disappeared on exchange with D_2O], 1.90-2.07 (m, 2 H), 2.30-2.42 (m, 1 H), 3.93-4.04 (m, 1 H), 4.76-4.88 (m, 2 H), [irradiation of the $=\text{CH}_2$ signal caused the width of the $\text{CH}(\text{OH})$ multiplet to decrease by 6.6 Hz.]; ^{13}C NMR (CD_2Cl_2 , 75.5 MHz) δ 23.89 (t'), 26.83 (t'), 29.73 (t'), 36.17 (t'), 68.96 (d'), 78.21 (s'), 107.17 (s'), 201.10 (s'); exact mass m/z calcd for $\text{C}_8\text{H}_{12}\text{O}$ 124.08881, found 124.08886.

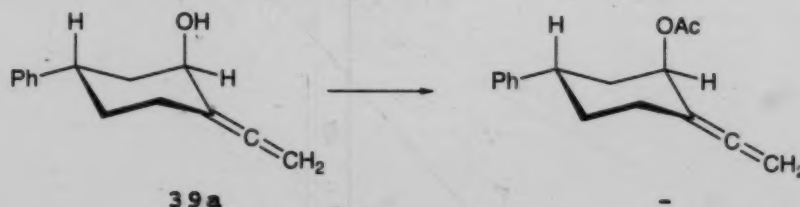
(b) Use of $\text{CF}_3\text{CO}_2\text{H}$.



(0.05 mL, 0.65 mmol) was added dropwise to a stirred and cooled (-78°C) solution of **38** (50.0 mg, 0.255 mmol) in CH_2Cl_2 (40 mL). The mixture was stirred for 30 min, Et_3N (0.05 mL) was added, and stirring was continued for 10 min. Evaporation of the solvent, and flash chromatography of the residue over silica gel (1.5 x 15 cm), using 2:8 EtOAc-hexane, gave **38a** (15.0 mg, 47%) as a pure (^1H NMR, 300 MHz), colorless oil, identical with material obtained in the previous experiment.

CDCl_3) a signal for C(1)H at δ 5.57 (dd, $J = 2.8, 2.8$ Hz), and we conclude, therefore that the acetate is axial.

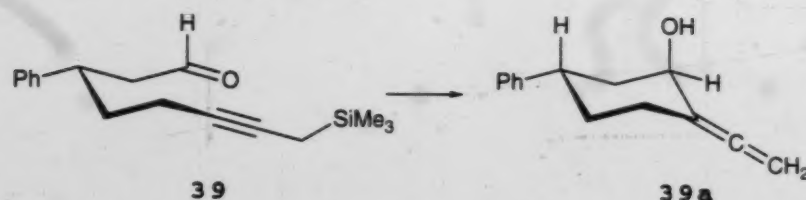
Derivatization of 39a: Trans-2-Ethenylidene-5-phenyl-1-cyclohexyl Acetate.



Ac_2O (0.014 mL, 0.15 mmol), Et_3N (0.025 mL, 0.18 mmol), and DMAP (0.5 mg, 0.004 mmol) were added to a stirred solution of **39a** (8.0 mg, 0.040 mmol) in CH_2Cl_2 (3 mL). Stirring was continued for 1 h and the mixture was then filtered through a pad (1.5 x 1 cm) of flash chromatography silica gel, using CH_2Cl_2 (20 mL) as a rinse. Evaporation of the combined filtrates, and flash chromatography of the residue over silica gel (1 x 10 cm), using 1:10 EtOAc-hexane, gave the derived acetate (8.5 mg, 88%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1962, 1738, 1234 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.66 (dddd, $J = 13.0, 13.0, 13.0, 4.1$ Hz, 1 H), 1.84 (ddd, $J = 13.6, 13.0, 2.8$ Hz, 1 H), 1.95-2.08 (m, 1 H), 2.08-2.23 [m, including singlet at δ 2.12 (3 H), 4 H], 2.34 (ddd, $J = 13.0, 3.4, 3.4$ Hz, 1 H), 2.47 (ddd, $J = 13.6, 4.1, 4.1$ Hz, 1 H), 3.02 (dddd, $J = 13.0, 13.0, 3.4, 3.4$ Hz, 1 H), 4.75 (d, $J = 4.1$ Hz, 2 H), 5.57 (dd, $J = 2.8, 2.8$ Hz, 1 H), 7.16-7.38 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ

21.47 (q'), 27.02 (t'), 33.92 (t') 37.94 (d'), 38.57 (t'), 72.16 (d'), 74.82 (t'), 98.62 (s'), 126.36 (d'), 126.90 (d'), 128.55 (d'), 147.75 (s'), 170.12 (s'), 205.11 (s'); exact mass m/z calcd for $C_{16}H_{18}O_2$ 242.13068, found 242.13060.

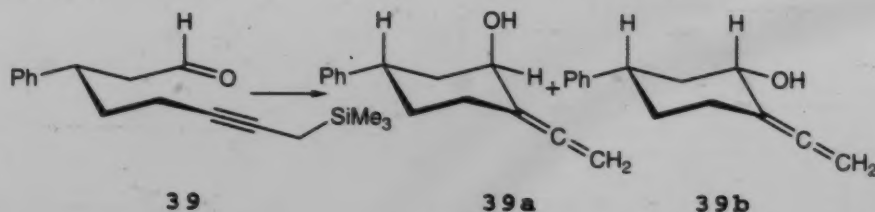
(b) Use of CF_3CO_2H .



TFA (0.01 mL, 0.13 mmol, in 1.0 mL CH_2Cl_2) was added dropwise to a stirred and cooled ($-78^\circ C$) solution of **39** (31.7 mg, 0.116 mmol) in CH_2Cl_2 (25 mL). The mixture was stirred for 1 h, Et_3N (0.05 mL) was added, and stirring was continued for 10 min. Evaporation of the solvent, and flash chromatography of the residue over silica gel (1.5 x 12 cm), using 2:8 EtOAc-hexane, gave **39a** (10.8 mg, 46%) as a pure (^1H NMR, 300 MHz), colorless oil, identical with material obtained by use of $ZnCl_2$.

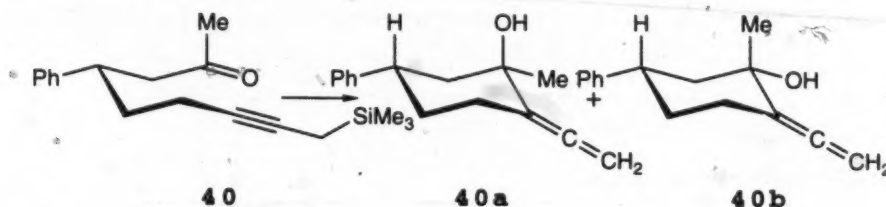
Trans-2-Ethenylidene-5-phenylcyclohexanol (39a)
and **Cis-2-Ethenylidene-5-phenylcyclohexanol (39b)**.

Use of Bu_4NF .



TBAF (1 M in THF, 0.51 mL, 0.51 mmol) was added dropwise to a stirred and cooled (0 °C) mixture of **39** (93.0 mg, 0.342 mmol) in THF (40 mL) and powdered molecular sieves (4Å, 2.50 g). The mixture was stirred at 0 °C for 1 h, diluted with Et₂O (20 mL), and filtered through a pad (2.5 x 2 cm) of flash chromatography silica gel, using Et₂O (50 mL) as a rinse. Evaporation of the solvent, and flash chromatography of the residue over silica gel (3 x 20 cm), using 1.5:8.5 EtOAc-hexane, gave **39a** (14.0 mg, 20%) as a pure (¹H NMR, 300 MHz), colorless oil, which was identified by comparison of its ¹H NMR spectrum with that of material obtained by use of ZnCl₂, and **39b** (25.5 mg, 37%) as a pure (¹H NMR, 300 MHz), colorless oil: FTIR (CH₂Cl₂, cast) 3396, 1962 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.47-1.66 (m, 2 H), 1.90-2.01 [(m, 2 H, including doublet at δ 1.96 (*J* = 4.9 Hz, 1 H)], 2.11-2.27 (m, 1 H), 2.35 (dddd, *J* = 11.9, 4.8, 2.8, 1.6 Hz, 1 H), 2.56 (ddd, *J* = 13.0, 5.1, 2.3 Hz, 1 H), 2.71 (dddd, *J* = 11.9, 11.9, 2.8, 2.8 Hz, 1 H), 4.09-4.21 (m, 1 H), 4.94-5.08 (m, 2 H), 7.18-7.35 (m, 5 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 29.78 (t'), 34.15 (t'), 42.55 (d'), 43.22 (t'), 68.25 (d'), 80.16 (t'), 106.74 (s'), 126.38 (d'), 126.82 (d'), 128.55 (d'), 145.39 (s'), 199.77 (s'); exact mass *m/z* calcd for C₁₄H₁₆O 200.12012, found 200.12021.

Trans-2-Ethenylidene-1-methyl-5-phenylcyclohexanol (40a) and Cis-2-Ethenylidene-1-methyl-5-phenylcyclohexanol (40b). Use of Bu_4NF .



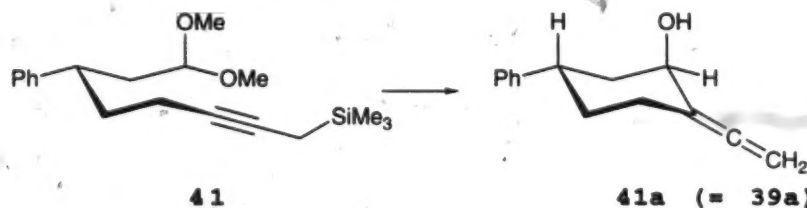
TBAF (1 M in THF, 0.31 mL, 0.31 mmol) was added dropwise to a stirred and cooled (0 °C) mixture of **40** (70.0 mg, 0.244 mmol) in THF (40 mL) and powdered molecular sieves (4 Å, 2.50 g). The mixture was stirred at 0 °C for 1 h, diluted with Et_2O (ca. 20 mL), and filtered through a pad (2.5 x 2 cm) of flash chromatography silica gel, using Et_2O (ca. 50 mL) as a rinse. Evaporation of the solvent, and flash chromatography of the residue over silica gel (2 x 15 cm), using 1.5:8.5 EtOAc -hexane, gave **40a** (35.0 mg, 67%) and **40b** (4.0 mg, 8%), each as a pure (^1H NMR, 300 MHz), colorless oil.

Alcohol **40a** had: FTIR (CH_2Cl_2 cast) 3355, 1958 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.41 (s, 3 H), 1.46-1.70 [m, 3 H, including singlet at δ 1.51 (1 H)], 1.95-2.10 (m, 2 H), 2.34 (ddd, $J = 13.8, 4.8, 2.4$ Hz, 1 H), 2.55-2.71 (m, 1 H), 3.14 (dddd, $J = 12.2, 12.2, 3.4, 3.4$ Hz, 1 H), 4.75 (dd, $J = 9.9, 4.5$ Hz, 1 H), 4.79 (dd, 9.9, 4.0 Hz, 1 H), 7.15-7.37 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 27.96 (t'), 29.43 (q'), 33.92 (t'), 39.20 (d'), 47.45 (t'), 70.13 (s'), 75.96 (t'), 106.10 (s'), 126.14 (d'), 127.00 (d'), 128.45 (d'), 146.33 (s'),

202.77 (s'); exact mass m/z calcd for $C_{15}H_{18}O$ 214.13577, found 214.13574.

Alcohol **40b** had: FTIR (CH_2Cl_2 cast) 3442, 1960 cm^{-1} ; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.49 (s, 3 H), 1.58 (dddd, $J = 12.7$, 12.7, 12.7, 4.2 Hz), 1 H), 1.77 (br dd, $J = 12.7$, 12.7 Hz, 1 H), 1.94-2.11 [m, 3 H, including singlet at δ 2.07 (1 H)], 2.24-2.39 (m, 1 H), 2.50 (ddd, $J = 12.7$, 4.8, 2.2 Hz, 1 H), 2.78 (dddd, $J = 12.7$, 12.7, 3.4, 3.4 Hz, 1 H), 4.92 (dd, $J = 9.9$, 4.3 Hz, 1 H), 4.99 (dd, $J = 9.9$, 3.9 Hz, 1 H), 7.17-7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 26.80 (q'), 29.29 (t'), 34.55 (t'), 41.97 (d'), 48.59 (t'), 70.07 (s'), 79.19 (t'), 109.88 (s'), 126.39 (d'), 126.85 (d'), 128.56 (d'), 145.52 (s'), 200.17 (s'); exact mass m/z calcd for $C_{15}H_{18}O$ 214.13577, found 214.13536.

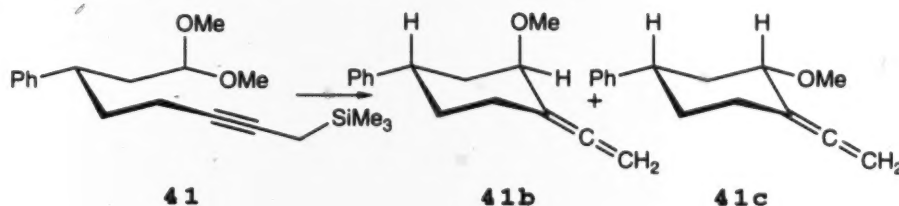
Trans-2-Ethenylidene-5-phenylcyclohexanol (41a)
[= 39a]. Use of a catalytic amount of $Me_3SiOSO_2CF_3$ at $-78^\circ C$ to room temperature.



$Me_3SiOSO_2CF_3$ (0.0062 M in CH_2Cl_2 , 0.20 mL, 0.00124 mmol) was added dropwise to a stirred and cooled ($-78^\circ C$) solution of **41** (3.5 mg, 0.011 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 6 h, the cold bath was removed, and stirring

was continued for another 5 h. The mixture was poured into a saturated aqueous NaHCO_3 (ca. 3.0 mL) and extracted with Et_2O (2 x 5 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried (MgSO_4), and evaporated. Flash chromatography of the residue over silica gel (1 x 10 cm), using 2:10 EtOAc-hexane, gave **41a** (1.7 mg, 77%) as a pure (^1H NMR, 300 MHz), colorless oil, identical with material (**39a**) obtained from **39**.

Trans-1-Ethenylidene-2-methoxy-4-phenylcyclohexane (41b), and *Cis*-1-Ethenylidene-2-methoxy-4-phenylcyclohexane (41c). Use of 1.1 equiv of $\text{Me}_3\text{SiOSO}_2\text{CF}_3$ at -78°C .

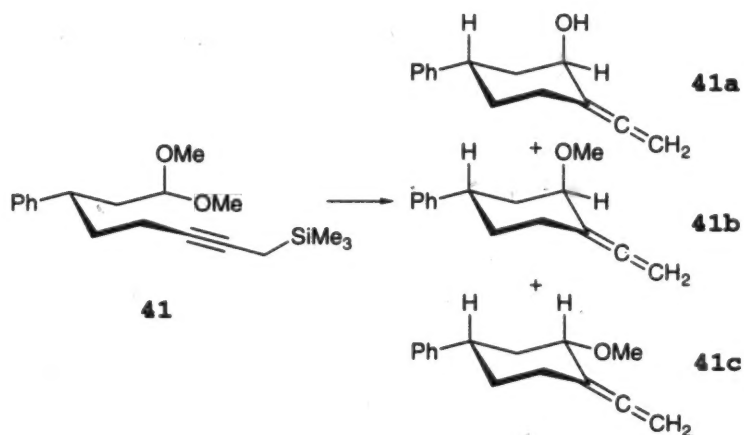


Me₃SiOSO₂CF₃ (0.0517 M in CH₂Cl₂, 2.75 mL, 0.142 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **41** (39.4 mg, 0.124 mmol) in CH₂Cl₂ (30 mL). Stirring was continued for 3 h, and saturated aqueous NaHCO₃ (10 mL) was added, the cold bath was removed, and stirring was continued for 30 min. The mixture was extracted with CH₂Cl₂ (2 x 10 mL), and the combined organic extracts were washed with water (20 mL) and brine (20 mL), dried (MgSO₄), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15

cm), using 0.5:9.5 EtOAc-hexane, gave **41b** (15.3 mg, 58%) as a pure (^1H NMR, 300 MHz), colorless oil and **41c** (7.1 mg, 27%) as a pure (^1H NMR, 300 MHz), colorless oil: Compound **41b** had: FTIR (CH_2Cl_2 cast) 1960 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.64 (dddd, $J = 12.6, 12.6, 12.6, 4.2\text{ Hz}$, 1 H), 1.81 (ddd, $J = 13.1, 13.1, 2.8\text{ Hz}$, 1 H), 1.91-2.02 (m, 1 H), 2.13-2.23 (m, 1 H), 2.28 (br ddd, $J = 13.1, 13.1, 3.4\text{ Hz}$, 1 H), 2.33-2.48 (m, 1 H), 3.06 (dddd, $J = 12.6, 12.6, 3.2, 3.2\text{ Hz}$, 1 H), 3.33 (s, 3 H), 3.98 (dd, $J = 2.8, 2.8\text{ Hz}$, 1 H), 4.72 (d, $J = 4.2\text{ Hz}$, 2 H), 7.17-7.37 (m, 5 H); ^{13}C NMR (CDCl_3 , 100.6 MHz) δ 26.32 (t'), 34.00 (t'), 37.67 (d'), 39.88 (t'), 55.56 (d'), 73.64 (t'), 78.64 (q'), 98.73 (s'), 126.10 (d'), 126.97 (d'), 128.42 (d'), 146.51 (s'), 204.89 (s'); exact mass m/z calcd for $\text{C}_{15}\text{H}_{18}\text{O}$ 214.13577, found 214.13534.

Compound **41c** had: FTIR (CH_2Cl_2 cast) 1962 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.51-1.72 (m, 2 H), 1.90-2.00 (m, 1 H), 2.08-2.22 (m, 1 H), 2.29-2.39 (m, 1 H), 2.49 (ddd, $J = 13.2, 4.3, 2.3\text{ Hz}$, 1 H), 2.69 (dddd, $J = 12.3, 12.3, 2.8, 2.8\text{ Hz}$, 1 H), 3.48 (s, 3 H), 3.69-3.79 (m, 1 H), 4.88 (ddd, 9.2, 4.2, 3.9 Hz, 1 H), 4.91 (ddd, 9.2, 3.2, 3.2 Hz, 1 H), 7.16-7.37 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 30.63 (t'), 34.55 (t'), 40.48 (t'), 42.95 (d'), 57.38 (d'), 77.10 (t'), 78.60 (q'), 103.49 (s'), 126.35 (d'), 126.78 (d'), 126.53 (d'), 145.49 (s'), 201.50 (s'); exact mass m/z calcd for $\text{C}_{15}\text{H}_{18}\text{O}$ 214.13577, found 214.13551.

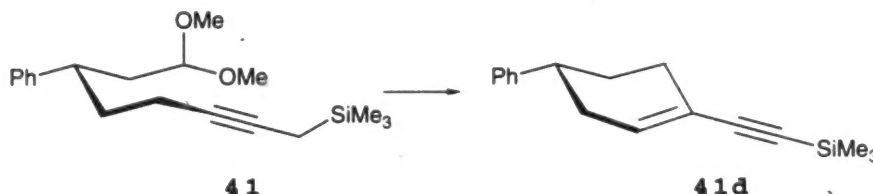
Trans-2-Ethenylidene-5-phenylcyclohexanol (**41a**), *Trans*-1-Ethenylidene-2-methoxy-4-phenylcyclohexane (**41b**), and *Cis*-1-Ethenylidene-2-methoxy-4-phenylcyclohexane (**41c**). Use of a catalytic amount of $\text{Me}_3\text{SiOSO}_2\text{CF}_3$ at -78°C .



$\text{Me}_3\text{SiOSO}_2\text{CF}_3$ (0.0062 M in CH_2Cl_2 , 0.18 mL, 0.0011 mmol) was added dropwise to a stirred and cooled (-78°C) solution of **41** (3.4 mg, 0.011 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 3 h, saturated aqueous NaHCO_3 (ca. 3.0 mL) was added, the cold bath was removed, and stirring was continued for ca. 30 min. The mixture was extracted with Et_2O (2 x 5 mL), and the combined organic extracts were washed with water (5 mL) and brine (5 mL), dried (MgSO_4), and evaporated. Flash chromatography of the residue over silica gel (1 x 10 cm), using 2:10 EtOAc-hexane, gave **41a** (0.9 mg, 48% based on conversion) as a pure (^1H NMR, 300 MHz), colorless oil, and a mixture (1.0 mg) of **41b**, **41c**, and unreacted **41** in a ratio of **41**:**41b**:**41c** = 1.2:1:1.3] as a colorless oil. Compounds **41b**,

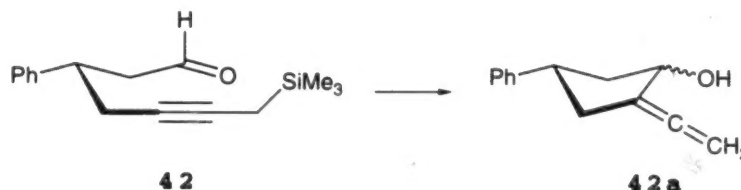
41c, and **41** were not further separated, identification being made through the ^1H NMR spectrum of the mixture.

Trimethyl[(4-phenyl-1-cyclohexen-1-yl)ethynyl]silane (41d).



CSA (15.0 mg, 0.0645 mmol) was added in one portion to a stirred solution of **41** (20.0 mg, 0.0629 mmol) in CH_2Cl_2 (30 mL). Stirring was continued for 48 h, Et_3N (1 mL) was added, and the solution was evaporated. Flash chromatography of the residue over silica gel (1.5 x 10 cm), using 1:20 EtOAc-hexane, gave **41d** (6.1 mg, 38%) as a pure (^1H NMR, 360 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 2144 cm^{-1} ; ^1H NMR (CDCl_3 , 360 MHz) δ 0.02 (s, 9 H), 1.70-1.82 (m, 1 H), 1.91-2.00 (m, 1 H), 2.17-2.46 (m, 4 H), 2.71-2.82 (m, 1 H), 6.24-6.29 (m, 1 H), 7.16-7.34 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 0.14 (q'), 29.51 (t'), 29.81 (t'), 33.81 (t'), 39.13 (d'), 91.65 (s'), 106.80 (s'), 120.77 (s'), 126.25 (d'), 126.85 (d'), 128.49 (d'), 135.56 (d'), 146.36 (s'); exact mass m/z calcd for $\text{C}_{17}\text{H}_{22}\text{Si}$ 254.14908, found 254.14893.

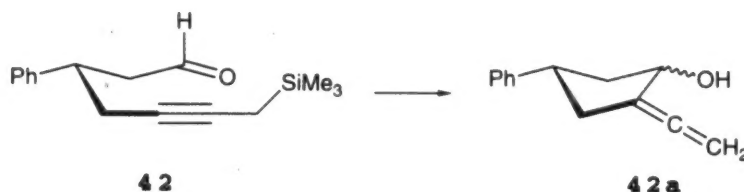
Cis- and Trans-2-Ethenylidene-4-phenylcyclopentanol (42a). (a) use of Bu_4NF .



TBAF (1M in THF, 0.27 mL, 0.27 mmol) was added dropwise to a stirred and cooled (0 °C) mixture of **42** (46.5 mg, 0.18 mmol) in THF (60.0 mL) and powdered 3Å molecular sieves (1.50 g). The mixture was stirred at 0 °C for 1 h, diluted with Et_2O (ca. 20 mL), and filtered through a pad (2.5 x 2 cm) of flash chromatography silica gel, which was rinsed with Et_2O (ca. 50 mL). Evaporation of the combined filtrates, and flash chromatography of the residue over silica gel (2 x 15 cm), using 2:8 EtOAc-hexane, gave **42a** (26.3 mg, 78%) as a colorless oil, which was a 55:45 mixture of epimers: FTIR (CH_2Cl_2 cast) 3356, 1959 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.73-2.00 (m, 2 H), 2.17-2.27 (m, 0.45 H), 2.45-2.60 (m, 1 H), 2.63-2.79 (m, 0.55 H), 2.79-2.92 (m, 0.55 H), 2.92-3.05 (m, 0.45 H), 3.05-3.19 (m, 0.55 H), 3.49-3.62 (m, 0.45 H), 4.78-5.04 (m, 3 H), 7.18-7.39 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 37.09 (t'), 37.30 (t'), 41.62 (d'), 42.72 (d'), 43.08 (t'), 43.51 (t'), 73.91 (d'), 74.68 (d'), 77.76 (t'), 79.26 (t'), 106.77 (s'), 106.87 (s'), 126.39 (d'), 126.51 (d'), 126.98 (d'), 127.07 (d'), 128.51 (d'), 128.55 (d'), 143.44 (s'),

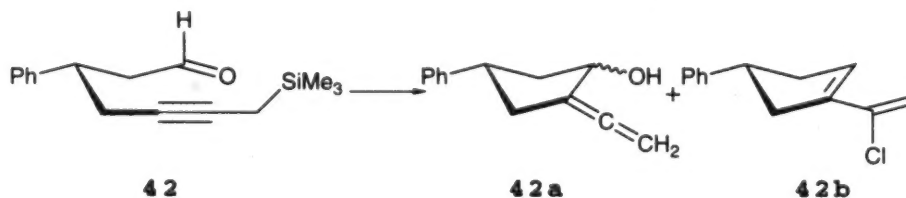
143.73 (s'), 202.39 (s'), 203.71 (s'); exact mass m/z calcd for $C_{13}H_{14}O$ 186.10446, found 186.10406.

(b) Use of $Sc(OSO_2CF_3)_3$.



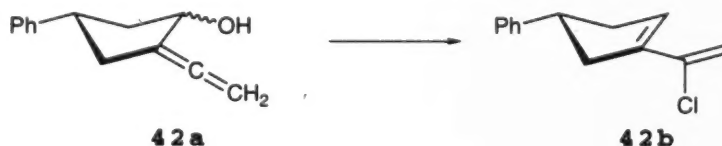
Aldehyde **42** (32.9 mg, 0.128 mmol) in $MeNO_2$ (5 mL) was added to a stirred solution of $Sc(OSO_2CF_3)_3$ (6.3 mg, 0.0128 mmol) in $MeNO_2$ (10 mL). Stirring was continued for 12 h, and the mixture was poured into brine (ca. 15 mL), and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 2:10 EtOAc-hexane, gave **42a** (16.8 mg, 70%) as a colorless oil, which was a 1:1 mixture of epimers. The structures were identified by examination of the ^1H NMR spectrum ($CDCl_3$, 300 MHz) of the mixture.

Cis- and Trans-2-Ethenylidene-4-phenylcyclopentanol (42a) and 1-(1-Chloroethenyl)-4-phenylcyclopentene (42b). Use of $ZnCl_2$.



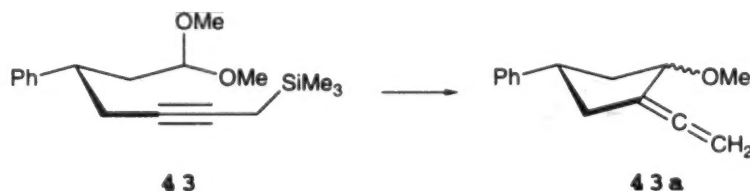
A solution of **42** (50.9 mg, 0.197 mmol) in CH_2Cl_2 (5 mL) was added to a stirred and cooled ($0\text{ }^\circ\text{C}$) suspension of ZnCl_2 (59.1 mg, 0.434 mmol) in CH_2Cl_2 (35 mL). The mixture was stirred for 2.5 h, the cold bath was removed, and stirring was continued for 12 h. The mixture was diluted with Et_2O (ca. 20 mL) and filtered through a pad (2 x 2 cm) of flash chromatography silica gel, using Et_2O (ca. 40 mL). Evaporation of the combined filtrates, and flash chromatography of the residue over silica gel (2 x 15 cm), using first hexane and then 2:8 EtOAc -hexane, gave **42a** (10.1 mg, 26%) as a colorless oil, which was a 55:45 mixture of epimers, identified by its ^1H NMR spectrum (CDCl_3 , 360 MHz), and **42b** (25.0 mg, 62%) as a pure (^1H NMR, 360 MHz), colorless oil. Compound **42b** had: FTIR (CH_2Cl_2 cast) unexceptional; ^1H NMR (CDCl_3 , 360 MHz) δ 2.57-2.71 (m, 2 H), 2.93-3.06 (m, 2 H), 3.57-3.67 (m, 1 H), 5.25 (br s, 1 H), 5.35 (br s, 1 H), 6.22 (br s, 1 H), 7.18-7.37 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 41.28 (t'), 41.57 (t'), 44.18 (d'), 112.61 (t'), 126.24 (d'), 126.87 (d'), 128.58 (d'), 132.16 (d'), 136.32 (s'), 139.46 (s'), 146.37 (s'); exact mass m/z calcd for $\text{C}_{13}\text{H}_{13}^{37}\text{Cl}$ 206.06763, found 206.06751.

1-(1-Chloroethenyl)-4-phenylcyclopentene (42b).



A solution of alcohols **42a** (15.0 mg, 0.081 mmol) in CH_2Cl_2 (2.0 mL) was added to a stirred suspension of ZnCl_2 (12.0 mg, 0.088 mmol) in CH_2Cl_2 (20 mL). Stirring was continued for 24 h, and the resulting solution was filtered through a pad (2 x 2 cm) of flash chromatography silica gel, using Et_2O (30 mL) as a rinse. Evaporation of the solvent, and flash chromatography of the residue over silica gel (1.5 x 10 cm), using hexane, gave **42b** (7.5 mg, 45%) as a pure (^1H NMR, 360 MHz), colorless oil, identified by its ^1H NMR spectrum.

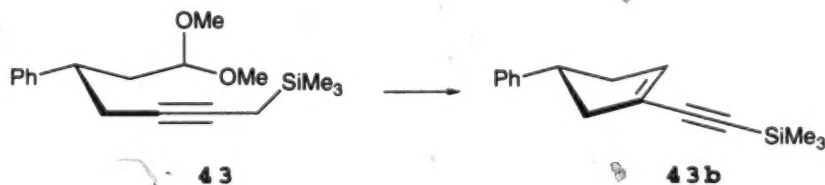
Trans- and Cis-1-Ethenylidene-2-methoxy-4-phenylcyclopentane (43a).



$\text{Me}_3\text{SiOSO}_2\text{CF}_3$ (0.0517 M in CH_2Cl_2 , 4.34 mL, 0.224 mmol) was added dropwise to a stirred and cooled (-78°C) solution of **43** (62.0 mg, 0.204 mmol) in CH_2Cl_2 (30 mL). Stirring was continued for 1.5 h, saturated aqueous NaHCO_3 (10 mL) was added, and the cold bath was removed. The mixture was stirred for 30 min, and extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried (MgSO_4), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm),

using 1:10 EtOAc-hexane, gave **43a** (36.4 mg, 89%) as a colorless oil, which was as a 3:2 mixture of epimers: FTIR (CH_2Cl_2 cast) 1958 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.76-1.96 (m, 1 H), 2.26 (br dd, $J = 13.2, 6.0\text{ Hz}$, 0.6 H), 2.43-2.80 (m, 1.8 H), 2.91-3.20 (m, 1 H), 3.38 (s, 1.8 H), 3.43 (s, 1.2 H), 3.45-3.57 (m, 0.6 H), 4.32 (br d, $J = 5.1\text{ Hz}$, 0.6 H), 4.41-4.48 (m, 0.4 H), 4.83-4.90 (m, 2 H), 7.17-7.37 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 36.96 (t'), 37.98 (t'), 40.68 (t'), 42.01 (t'), 42.72 (d'), 42.87 (d'), 55.98 (q'), 56.78 (q'), 76.15 (t'), 76.87 (t'), 82.86 (d'), 83.96 (d'), 101.97 (s'), 103.04 (s'), 126.29 (d'), 126.42 (d'), 127.06 (d'), 128.46 (d'), 128.49 (d'), 143.70 (s'), 144.19 (s'), 203.93 (s'), 204.99 (s'); exact mass calcd for $\text{C}_{14}\text{H}_{16}\text{O}$ 200.12012, found 200.12014.

Trimethyl[(4-phenyl-1-cyclopenten-1-yl)ethynyl]silane (43b**).**



A solution of **43** (31.7 gm, 0.104 mmol) in CH_2Cl_2 (ca. 2 mL) was added to a stirred solution of CSA (26.6 mg, 0.115 mmol) in CH_2Cl_2 (30 mL). Stirring was continued for 20 h, Et_3N (1 mL) was added, and the solution was evaporated. Flash chromatography of the residue over silica gel (1.5 x 15

cm), using 1:20 EtOAc-hexane, gave **43b** (8.6 mg, 34%) as a pure (^1H NMR, 360 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 2146 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.21 (s, 9 H), 2.42-2.62 (m, 2 H), 2.78-2.93 (m, 2 H), 3.46 (dddd, $J = 8.4, 8.4, 8.4, 8.4\text{ Hz}$, 1 H), 6.10-6.19 (m, 1 H), 7.15-7.34 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 0.06 (q'), 41.77 (t'), 43.49 (d'), 44.53 (t'), 95.59 (s'), 102.12 (s'), 123.91 (s'), 126.17 (d'), 126.92 (d'), 128.53 (d'), 137.98 (d'), 146.16 (s'); exact mass calcd for $\text{C}_{16}\text{H}_{20}\text{Si}$ 240.13342, found 240.13362.

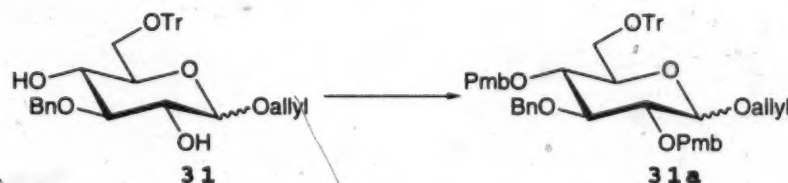
Cis-2-Ethenylidene-1-methyl-4-phenylcyclopentanol and Trans-2-Ethenylidene-1-methyl-4-phenylcyclopentanol (44a).



TBAF (1 M in THF, 0.14 mL, 0.14 mmol) was added dropwise to a stirred and cooled (0 °C) mixture of **44** (31.2 mg, 0.114 mmol) in THF (40 mL) and powdered 3Å molecular sieves (0.50 g). The mixture was stirred at 0 °C for 1 h. Saturated aqueous NH_4Cl (ca. 10 mL) was added and, after 5 min, the organic phase was washed with water (10 mL) and brine (10 mL), dried (MgSO_4), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 12 cm), using 1.5:8.5 EtOAc-hexane, gave **44a** (20.2 mg, 88%) as a colorless oil,

which was a 1:7.2 mixture of epimers: FTIR (CH_2Cl_2 cast) 3367, 1958 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 1.50 (s, 3 H), 1.60 (br s, 0.12 H), 1.65 (br s, 0.88 H), 1.80 (dd, $J = 12.7, 12.7$ Hz, 0.88 H), 2.09 (dd, $J = 12.2, 12.2$ Hz, 0.12 H), 2.29 (ddd, $J = 12.8, 6.2, 1.7$ Hz, 1 H), 2.55-2.67 (m, 0.88 H), 2.73-2.92 (m, 0.24 H), 2.97-3.08 (m, 0.88 H), 3.16 (dddd, $J = 11.5, 11.5, 7.0, 7.0$ Hz, 0.12 H), 3.50-3.62 (m, 0.88 H), 4.88-5.01 [m, 2 H, including two sets of doublets at δ 4.93 ($J = 3.4$ Hz) and δ 4.94 ($J = 3.4$ Hz)], 7.18-7.36 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 27.05 (q'), 28.87 (q'), 37.66 (t'), 37.77 (t'), 42.47 (d'), 49.30 (t'), 79.15 (t'), 79.58 (t'), 110.53 (s'), 126.34 (d'), 126.47 (d'), 127.02 (d), 127.08 (d'), 128.47 (d'), 128.54 (d'), 143.58 (s'), 143.73 (s'), 201.52 (s'), 202.12 (s'); exact mass calcd for $\text{C}_{14}\text{H}_{16}\text{O}$ 200.12012, found 200.12000.

2-Propenyl 2,4-Bis-O-[(4-methoxyphenyl)methyl]-3-O-(phenylmethyl)-6-O-(triphenylmethyl)-D-glucopyranoside (31a).

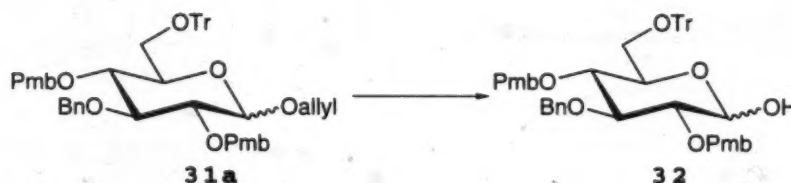


NaH (80% dispersion in oil, 10.0 g, 333.0 mmol) was added portionwise to a stirred and cooled (0°C) solution of diols **31**^{17, 40} (30.02 g, 54.38 mmol) in THF (450 mL) over 5

min. The mixture was stirred (Ar atmosphere) for 30 min, and then *p*-methoxybenzyl chloride (45.0 mL, 333.0 mmol) was added neat in one portion by syringe. Stirring was continued at 0 °C for 15 min. The cold bath was removed, and the solution was allowed to warm to room temperature and then refluxed for 24 h. The mixture was cooled to 0 °C and the excess of NaH was carefully decomposed by addition of MeOH (ca. 50 mL). The mixture was filtered through a pad (5 x 4 cm) of Celite which was rinsed with Et₂O (ca. 200 mL), and the solvent was evaporated. Flash chromatography of the residue over silica gel (6 x 35 cm), using 1.5:8.5 to 2:8 EtOAc-hexane, gave **31a** (39.37 g, 91%) as a pure (¹H NMR, 400 MHz), off-white solid, which was a mixture of epimers: mp 41-43 °C; [α]_D = 8.8 (c 2.07, CHCl₃); FTIR (CHCl₃ cast) unexceptional; ¹H NMR (CDCl₃, 400 MHz) δ 3.15-3.25 (m, 1 H), 3.35-3.50 (m, 1 H), 3.53-3.64 (m, 2 H), 3.73-3.87 (m, including singlets at δ 3.76, 3.77, 3.81 and 3.83, 7 H), 3.92-3.99 (m, 0.65 H), 4.05-4.12 (m, 0.65 H), 4.20-4.31 (m, 2.05 H), 4.46-4.56 (m, 0.65 H), 4.56-4.83 (m, 4 H), 4.86-4.98 (m, 2 H), 5.21-5.46 (m, 2 H), 5.92-6.13 (m, 1 H), 6.66-6.90 (m, 6 H), 7.21-7.41 (m, 16 H), 7.45-7.55 (m, 6 H); ¹³C NMR (CDCl₃, 100.6 MHz) δ 55.23 (q'), 55.25 (q'), 62.46 (t'), 62.62 (t'), 67.96 (t'), 70.06 (t'), 70.50 (d'), 72.80 (t'), 74.64 (t'), 75.92 (t'), 77.62 (d'), 77.90 (d'), 79.91 (d'), 82.24 (d'), 82.31 (d'), 84.78 (d'), 86.32 (s'), 86.35 (s'), 95.29 (d'), 102.77 (d'), 113.62 (d'), 113.83 (d'), 117.34 (t'), 118.22 (t'), 126.79 (d'), 126.94 (d'), 127.54 (d'), 127.63 (d'), 127.78 (d'), 127.96 (d'),

128.08 (d'), 128.25 (d'), 128.41 (d'), 128.85 (d'), 129.20 (d'), 129.59 (d'), 129.78 (d'), 129.86 (d'), 130.12 (s'), 130.18 (s'), 130.50 (s'), 130.78 (s'), 133.94 (d'), 134.25 (d'), 138.74 (s'), 138.92 (s'), 144.00 (s'), 144.26 (s'), 159.15 (s'), 159.20 (s'), 159.27 (s'), 159.35 (s'); exact mass (HR electrospray) m/z calcd for $C_{51}H_{52}NaO_8$ ($M + Na$) 815.355989, found 815.355280. Anal. Calcd for $C_{51}H_{52}O_8$: C, 77.25; H, 6.61. Found: C, 77.39; H, 6.56.

2,4-Bis-O-[(4-methoxyphenyl)methyl]-3-O-(phenylmethyl)-6-O-(triphenylmethyl)-D-glucopyranose (32).

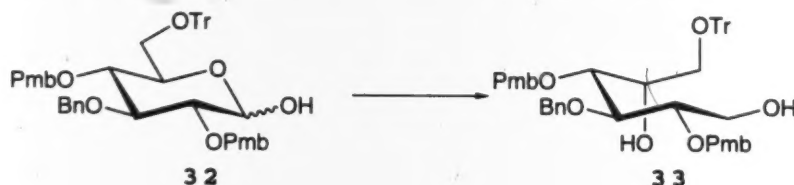


DMSO (45 mL) was added in one portion to a suspension of **31a** (9.68 g, 12.2 mmol) and *t*-BuOK (2.73 g, 24.4 mmol). The mixture was stirred to dissolve the solids and then heated at 100 °C for 1 h. The solution was allowed to cool to room temperature and then poured into water (150 mL). The orange mixture was extracted with CH₂Cl₂ (4 x 50 mL), and the combined organic extracts were washed with water (1 x 40 mL) and brine (1 x 30 mL), and evaporated. The solid residue was dissolved in 8:1 acetone-water (40 mL), and HgO (3.96 g, 18.3 mmol) was added to the solution (stirring). A solution of

HgCl_2 (4.97 g, 18.3 mmol) in 8:1 acetone-water (15 mL) was added dropwise, and stirring was continued for 4 h at room temperature. The mixture was filtered through a pad (5 x 4 cm) of Celite and the pad was rinsed with acetone (50 mL). The combined filtrates were evaporated and the residue was dissolved in CH_2Cl_2 (100 mL), washed with 20% aqueous NaI (1 x 100 mL), and brine (1 x 40 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (6 x 20 cm), using 1.5:8.5 EtOAc-hexane, gave **32** (8.07 g, 88%) as a pure (^1H NMR, 400 MHz), off-white solid, which was a mixture of epimers: mp 61-63 °C; $[\alpha]_D = 7.8$ (c 0.32, CHCl_3); FTIR (CDCl_3 cast) 3428 (br) cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 2.86 (d, $J = 2.1$ Hz, 0.27 H), δ 3.07 (d, $J = 5.3$ Hz, 0.64 H), δ 3.16-3.24 (m, 1 H), 3.40-3.47 (m, 1.35 H), 3.50-3.66 (m, 2 H), 3.67-3.81 (m, including singlets at δ 3.74, 3.78, 3.81, 7 H), 3.84-4.02 (m, 0.65 H), 4.25 (d, $J = 10.1$ Hz, 1 H), 4.57-4.63 (m, 1 H), 4.64-4.93 (m, 4.65 H), 5.30 (dd, $J = 2.8, 2.8$ Hz, 0.28 H), 6.65-6.75 (m, 4 H), 6.80-6.87 (m, 2 H), 7.18-7.39 (m, 16 H), 7.41-7.51 (m, 6 H); ^{13}C NMR (CD_3COCD_3 , 75.5 MHz) δ 55.41 (q'), 63.67 (t'), 63.81 (t'), 70.87 (d'), 72.48 (t'), 74.53 (t'), 74.78 (t'), 74.84 (t'), 75.31 (d'), 75.80 (t'), 75.86 (t'), 78.56 (d'), 78.68 (d'), 81.50 (d'), 82.58 (d'), 84.26 (d'), 85.62 (d'), 86.92 (s'), 91.45 (s'), 98.61 (d'), 114.10 (d'), 114.25 (d'), 114.36 (d'), 127.73 (d'), 127.99 (d'), 128.42 (d'), 128.51 (d'), 128.90 (d'), 129.59 (d'), 130.05 (d'), 130.21 (d'), 130.27 (d'), 130.31 (d'), 131.28 (s'), 131.44 (s'), 131.76 (s'), 132.11 (s'), 140.14 (s'),

140.29 (s'), 144.99 (s'), 145.04 (s'), 159.93 (s'), 159.99 (s'), 160.09 (s'); exact mass (HR electrospray) m/z calcd for $C_{48}H_{48}NaO_8$ ($M + Na$) 775.324689, found 775.324710. Anal. Calcd for $C_{48}H_{48}O_8$: C, 76.57; H, 6.42. Found: C, 76.18; H, 6.41.

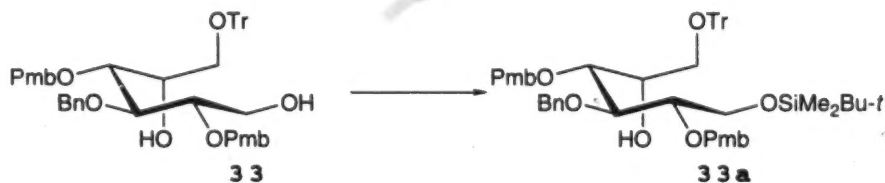
2,4-Bis-O-[(4-methoxyphenyl)methyl]-3-O-(phenylmethyl)-6-O-(triphenylmethyl)-D-glucitol (33).



$LiAlH_4$ (1.41 g, 37.2 mmol) was added in five portions to a stirred and cooled (0 °C) solution of **32** (10.27 g, 13.65 mmol) in THF (200 mL). The cold bath was removed and stirring was continued for 4 h. The solution was recooled to 0 °C, and water (1.4 mL), 15% aqueous NaOH (1.4 mL), and water (4.2 mL) were added sequentially. The cold bath was removed and the solution was stirred for 30 min, and then filtered through a pad (6 x 6 cm) of Celite. The pad was rinsed with Et_2O (500 mL) and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (6 x 20 cm), using 1:3 to 4:6 EtOAc-hexane, gave **33** (9.64 g, 93%) as a pure (^1H NMR, 400 MHz), white solid: mp 44-46 °C; $[\alpha]_D = -6.78$ (c 1.15, $CHCl_3$); FTIR ($CHCl_3$ cast) 3460 (br) cm^{-1} ; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.12 (t, $J = 6.5$ Hz, 1 H), 3.12 (d, $J = 5.1$ Hz, 1 H), 3.28 (dd, $J = 9.5, 5.3$ Hz, 1 H),

3.36 (dd, $J = 9.5, 4.3$ Hz, 1 H), 3.50-3.57 (m, 1 H), 3.65-3.72 (m, 1 H), 3.73-3.86 (m, including singlets at δ 3.78, 3.79, 9 H), 4.01-4.08 (m, 1 H), 4.33 (d, $J = 11.0$ Hz, 1 H), 4.35 (d, $J = 11.0$ Hz, 1 H), 4.48-4.60 (m, 3 H), 4.67 (d, $J = 11.3$ Hz, 1 H), 6.75-6.80 (m, 2 H), 6.81-6.85 (m, 2 H), 6.97-7.03 (m, 2 H), 7.17-7.34 (m, 16 H), 7.42-7.49 (m, 6 H); ^{13}C NMR (CD_3COCD_3 , 75.5 MHz) δ 55.45 (q'), 62.45 (t'), 66.47 (t'), 71.78 (d'), 73.04 (t'), 73.27 (t'), 74.89 (t'), 79.05 (d'), 80.10 (d'), 81.04 (d'), 87.27 (s'), 114.21 (d'), 114.34 (d'), 127.74 (d'), 128.09 (d'), 128.54 (d'), 128.60 (d'), 128.96 (d'), 129.70 (d'), 130.23 (d'), 131.63 (s'), 131.97 (s'), 140.03 (s'), 145.26 (s'), 160.01 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{48}\text{H}_{50}\text{NaO}_8$ ($M + \text{Na}$) 777.340339, found 777.340650. Anal. Calcd for $\text{C}_{48}\text{H}_{50}\text{O}_8$: C, 76.37; H, 6.68. Found: C, 76.15; H, 6.83.

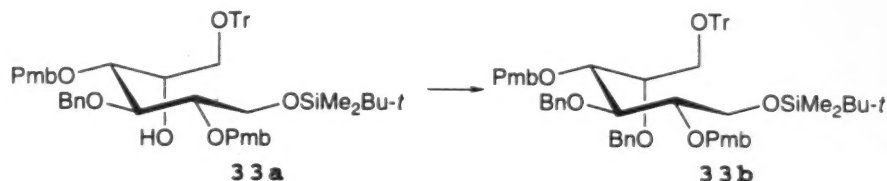
1-O-[(1,1-Dimethylethyl)dimethylsilyl]-2,4-bis-O-[(4-methoxyphenyl)methyl]-3-O-(phenylmethyl)-6-O-(triphenylmethyl)-D-glucitol (33a).



Et_3N (4.05 mL, 29.0 mmol) was added in one portion to a stirred solution of **33** (14.0 g, 18.6 mmol), DMAP (570 mg, 4.66 mmol), and $t\text{-BuMe}_2\text{SiCl}$ (4.18 g, 27.7 mmol) in CH_2Cl_2 (400

mL). Stirring was continued for 16 h, and the mixture was diluted with CH_2Cl_2 (200 mL), and washed with brine (2 x 200 mL). The organic extracts were dried and evaporated. Flash chromatography of the residue over silica gel (6 x 25 cm), using 1:10 EtOAc-hexane, gave **33a** (16.0 g, 99%) as a pure (^1H NMR, 400 MHz), gummy solid: $[\alpha]_D = 3.93$ (c 1.5, CHCl_3); FTIR (CH_2Cl_2 cast) 3510 (br) cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 0.03 (s, 6 H), 0.88 (s, 9 H), 3.12 (d, $J = 4.8$ Hz, 1 H), 3.27 (dd, $J = 9.5, 5.7$ Hz, 1 H), 3.34 (dd, $J = 9.8, 3.7$ Hz, 1 H), 3.65-3.84 (m, including singlets at δ 3.78 and 3.79, 11 H), 3.95-4.04 (m, 1 H), 4.34 (d, $J = 11.0$ Hz, 1 H), 4.38 (d, $J = 11.0$ Hz, 1 H), 4.53 (d, $J = 11.4$ Hz, 1 H), 4.55 (d, $J = 11.2$, 1 H), 4.60 (d, $J = 11.4$ Hz, 1 H), 4.64 (d, $J = 11.2$ Hz, 1 H), 6.73-6.80 (m, 2 H), 6.82-6.87 (m, 2 H), 6.95-7.02 (m, 2 H), 7.21-7.35 (m, 16 H), 7.42-7.50 (m, 6 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ -5.36 (q'), 18.21 (s'), 25.96 (q'), 55.20 (q'), 63.13 (t'), 64.97 (t'), 71.21 (d'), 72.53 (t'), 72.84 (t'), 74.00 (t'), 76.71 (d'), 78.32 (d'), 79.36 (d'), 86.58 (s'), 113.60 (d'), 113.70 (d'), 126.98 (d'), 127.67 (d'), 127.80 (d'), 128.29 (d'), 128.35 (d'), 128.80 (d'), 129.61 (d'), 129.74 (d'), 130.29 (s'), 130.70 (s'), 138.15 (s'), 144.02 (s'), 159.14 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{54}\text{H}_{64}\text{NaO}_8\text{Si}$ (M + Na) 891.426818, found 891.426920. Anal. Calcd for $\text{C}_{54}\text{H}_{64}\text{O}_8\text{Si}$: C, 73.24; H, 7.42. Found: C, 73.32; H, 7.46.

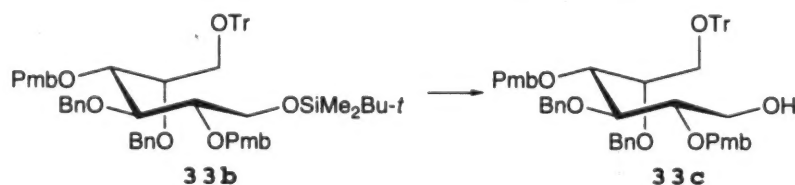
1-O-[(1,1-Dimethylethyl)dimethylsilyl]-2,4-bis-O-[(4-methoxyphenyl)methyl]-3,5-bis-O-(phenylmethyl)-6-O-(triphenylmethyl)-D-glucitol (**33b**).



NaH (80% dispersion in oil, 1.40 g, 46.0 mmol) was added in five portions to a stirred and cooled (0 °C) solution of **33a** (16.0 g, 18.4 mmol) in THF (500 mL). The resulting mixture was stirred for 30 min and then BnBr (5.50 mL, 46.0 mmol) was added neat in one portion by syringe. The cold bath was removed and the mixture was stirred for 1 h and then refluxed for 24 h. The resulting mixture was cooled (0 °C) and quenched with MeOH (50 mL), diluted with brine (200 mL), and extracted with Et₂O (3 x 300 mL). The combined organic extracts were washed with brine (1 x 200 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (6 x 35 cm), using 5:95 to 1:10 EtOAc-hexane, gave **33b** (17.0 g, 96%) as a pure (¹H NMR, 400 MHz), thick syrup: [α]_D = 5.71 (c 2.38, CHCl₃); FTIR (CH₂Cl₂ cast) unexceptional; ¹H NMR (CDCl₃, 400 MHz) δ -0.03 (s, 3 H), -0.01 (s, 3 H), 0.86 (s, 9 H), 3.37 (dd, *J* = 10.4, 5.6 Hz, 1 H), 3.56 (dd, *J* = 10.3, 2.6 Hz, 1 H), 3.60-3.70 (m, 3 H), 3.71-3.80 (m, including singlets at δ 3.74 and 3.76, 8 H), 4.01 (dd, *J* = 5.7, 5.7 Hz, 1 H), 4.35 (d, *J* = 11.6 Hz, 1 H), 4.43-4.72 (m,

7 H), 6.68-6.76 (m, 4 H), 6.92-6.97 (m, 2 H), 7.16-7.32 (m, 21 H), 7.41-7.46 (m, 6 H); ^{13}C NMR (CDCl_3 , 100.6 MHz) δ -5.40 (q'), 18.22 (s'), 25.98 (q'), 55.23 (q'), 63.24 (t'), 63.88 (t'), 72.16 (t'), 72.78 (t'), 73.48 (t'), 74.45 (t'), 78.26 (d'), 78.58 (d'), 79.65 (d'), 80.24 (d'), 86.77 (s'), 113.45 (d'), 113.67 (d'), 126.91 (d'), 127.29 (d'), 127.77 (d'), 128.14 (d'), 128.22 (d'), 128.88 (d'), 129.52 (d'), 129.66 (d'), 130.93 (s'), 131.11 (s'), 138.84 (s'), 138.89 (s'), 144.12 (s'), 158.91 (s'), 159.01 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{61}\text{H}_{70}\text{NaO}_8\text{Si}$ ($M + \text{Na}$) 981.473768 found 981.474400. Anal. Calcd for $\text{C}_{61}\text{H}_{70}\text{O}_8\text{Si}$: C, 76.38; H, 7.36. Found: C, 76.50; H, 7.51.

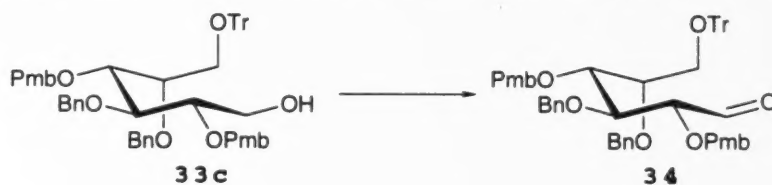
2,4-Bis-O-[(4-methoxyphenyl)methyl]-3,5-bis-O-(phenylmethyl)-6-O-(triphenylmethyl)-D-glucitol (33c).



TBAF (1 M in THF, 17.75 mL, 17.75 mmol) was added in one portion by syringe to a stirred solution of **33b** (16.67 g, 17.40 mmol) in THF (340 mL). The mixture was stirred for 4 h at room temperature, diluted with Et_2O (150 mL), and washed with water (1 x 150 mL). The aqueous layer was extracted with Et_2O (2 x 90 mL) and the combined organic extracts were washed with brine (1 x 150 mL), dried, and evaporated. Flash

chromatography of the residue over silica gel (6 x 35 cm), using 2:8 to 3:7 EtOAc-hexane, gave **33c** (13.50 g, 92%) as a pure (^1H NMR, 400 MHz), white solid: mp 41-43 °C; $[\alpha]_D = -11.90$ (c 2.66, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3476 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 2.12 (br s, 1 H), 3.41 (dd, $J = 11.3$, 3.8 Hz, 1 H), 3.51-3.61 (m, 2 H), 3.61-3.79 (m, including singlets at δ 3.74 and 3.77, 8 H), 3.79-3.88 (m, 2 H), 4.08 (dd, $J = 4.4$, 4.4 Hz, 1 H), 4.42 (d, $J = 11.3$ Hz, 1 H), 4.45-4.55 (m, 4 H), 4.61 (br s, 2 H), 4.75 (d, $J = 11.3$ Hz, 1 H), 6.75 (d, $J = 8.0$ Hz, 2 H), 6.80 (d, $J = 8.0$ Hz, 2 H), 7.00 (d, $J = 8.5$ Hz, 2 H), 7.16-7.35 (m, 21 H), 7.43-7.50 (m, 6 H); ^{13}C NMR (CDCl_3 , 100.6 MHz) δ 55.21 (q'), 61.93 (t'), 63.18 (t'), 72.19 (t'), 73.29 (t'), 74.39 (t'), 78.04 (d'), 78.76 (d'), 79.12 (d'), 79.26 (d'), 86.90 (s'), 113.54 (d'), 113.81 (d'), 126.95 (d'), 127.36 (d'), 127.58 (d'), 127.78 (d'), 128.15 (d'), 128.29 (d'), 128.83 (d'), 129.57 (d'), 129.68 (d'), 130.40 (s'), 130.52 (s'), 138.40 (s'), 138.67 (s'), 144.01 (s'), 159.05 (s'), 159.24 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{55}\text{H}_{56}\text{NaO}_8$ (M + Na) 867.387289, found 867.387600. Anal. Calcd for $\text{C}_{55}\text{H}_{56}\text{O}_8$: C, 78.17; H 6.68. Found: C, 78.14; H, 6.74.

2,4-Bis-O-[(4-methoxyphenyl)methyl]-3,5-bis-O-(phenylmethyl)-6-O-(triphenylmethyl)-D-glucose (34).



DMSO (0.91 mL, 12.8 mmol) was added dropwise to a stirred and cooled (-78°C) solution of $(\text{COCl})_2$ (0.84 mL, 9.62 mmol) in CH_2Cl_2 (40 mL). After 20 min, **33c** (2.69 g, 3.19 mmol) in CH_2Cl_2 (7 mL plus 3 mL as a rinse) was added by syringe over 1 min. Stirring was continued for 30 min at -78°C , and then Et_3N (3.65 mL, 26.2 mmol) was added dropwise over ca. 2 min. The cold bath was removed and stirring was continued for 6 h. The mixture was diluted with water (2 mL) and CH_2Cl_2 (50 mL), washed with brine (1 x 20 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (3 x 25 cm), using 1:9 to 2:8 EtOAc-hexane, gave **34** (2.39 g, 89%) as a pure (^1H NMR, 400 MHz), white solid: mp $46\text{--}48^{\circ}\text{C}$; $[\alpha]_{\text{D}} = 0.600$ (c 1.50, CHCl_3); FTIR (CH_2Cl_2 cast) 1727 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 3.28 (dd, $J = 10.3, 4.7\text{ Hz}$, 1 H), 3.64 (dd, $J = 10.3, 2.7\text{ Hz}$, 1 H), 3.70–3.79 (m, including singlets at δ 3.72 and 3.74, 7 H), 3.82 (d, $J = 5.2\text{ Hz}$, 1 H), 4.02–4.10 (m, 2 H), 4.24 (d, $J = 10.3\text{ Hz}$, 1 H), 4.30–4.43 (m, 4 H), 4.49 (d, $J = 11.6\text{ Hz}$, 1 H), 4.71 (dd, $J = 21.9, 11.6\text{ Hz}$, 2 H), 6.62–6.65 (m, 2 H), 6.75–6.82 (m, 4 H), 7.04–7.10 (m, 2 H), 7.15–7.23 (m, 14 H), 7.23–7.36 (m, 5 H), 7.40–7.45

(m, 6 H), 9.64 (s, 1 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 55.24 (q'), 55.27 (q'), 62.73 (t'), 72.22 (t'), 72.79 (t'), 73.07 (t'), 73.96 (t'), 76.64 (d'), 78.77 (d'), 80.04 (d'), 80.78 (d'), 86.86 (s'), 113.43 (d'), 113.93 (d'), 127.03 (d'), 127.25 (d'), 127.45 (d'), 127.86 (d'), 128.14 (d'), 128.38 (d'), 128.88 (d'), 129.55 (s'), 129.74 (d'), 130.03 (s'), 130.19 (d'), 137.91 (s'), 138.64 (s'), 143.99 (s'), 159.02 (s'), 159.50 (s'), 201.06 (d'); exact mass (HR electrospray) m/z calcd for $\text{C}_{55}\text{H}_{54}\text{NaO}_8$ ($M + \text{Na}$) 865.371639, found 865.371920. Anal. Calcd for $\text{C}_{55}\text{H}_{54}\text{O}_8$: C, 78.36; H, 6.46. Found: -C, 78.01; H, 6.52.

1,1-Dibromo-1,2-dideoxy-3,5-bis-O-[(4-methoxyphenyl)methyl]-4,6-bis-O-(phenylmethyl)-7-O-(triphenylmethyl)-D-gluco-hept-1-enitol (34a).

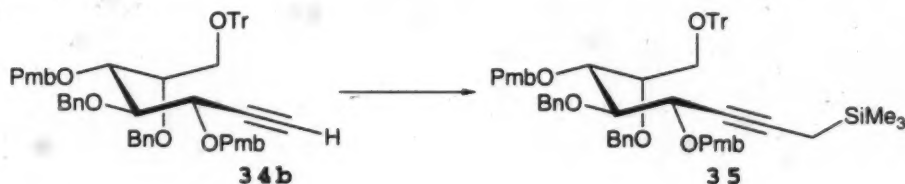


A solution of CBr_4 (1.36 g, 4.10 mmol) in CH_2Cl_2 (20 mL) was added at a fast dropwise rate to a stirred and cooled ($-20\text{ }^\circ\text{C}$) solution of Ph_3P (1.07 g, 4.08 mmol) in CH_2Cl_2 (20 mL). The resulting mixture was stirred for 15 min at $-20\text{ }^\circ\text{C}$, and then a solution of **34** (1.73 g, 2.05 mmol) and Et_3N (0.28 mL, 2.05 mmol) in CH_2Cl_2 (20 mL) was added dropwise at $-60\text{ }^\circ\text{C}$. The cold bath was removed and the solution was allowed to

warm to room temperature. After 30 min, the mixture was filtered through a pad (3 x 3 cm) of flash chromatography silica gel which was rinsed with Et₂O (50 mL), and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (1.5 x 25 cm), using 1:9 EtOAc-hexane, gave **34a** (1.70 g, 83%) as a pure (¹H NMR, 300 MHz), white solid: mp 39-41 °C; [α]_D = 17.1 (c 1.52, CHCl₃); FTIR (CHCl₃ cast) unexceptional; ¹H NMR (CDCl₃, 300 MHz) δ 3.36-3.46 (m, 2 H), 3.65-3.75 (m, including singlet at δ 3.73, 5 H), 3.78 (s, 3 H), 4.07 (dd, J = 5.5, 5.5 Hz, 1 H), 4.22 (dd, J = 8.4, 4.6 Hz, 1 H), 4.31 (d, J = 11.4 Hz, 1 H), 4.41 (d, J = 11.7 Hz, 1 H), 4.51-4.64 (m, 5 H), 4.70 (d, J = 11.6 Hz, 1 H), 6.60 (d, J = 8.5 Hz, 1 H), 6.72 (d, J = 8.5 Hz, 2 H), 6.81 (d, J = 9.0 Hz, 2 H), 6.99 (d, J = 9.0 Hz, 2 H), 7.18-7.36 (m, 21 H), 7.40-7.50 (m, 6 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 55.24 (q'), 63.19 (t'), 70.94 (t'), 72.43 (t'), 73.91 (t'), 74.96 (t'), 78.55 (d'), 79.03 (d'), 79.58 (d'), 79.74 (d'), 86.73 (s'), 92.29 (s'), 113.51 (d'), 113.82 (d'), 126.93 (d'), 127.38 (d'), 127.56 (d'), 127.79 (d'), 128.24 (d'), 128.29 (d'), 128.92 (d'), 129.68 (s'), 129.71 (d'), 129.85 (d'), 130.84 (s'), 137.57 (d'), 138.33 (s'), 138.77 (s'), 144.05 (s'), 158.98 (s'), 159.36 (s'); exact mass (HR electrospray) m/z calcd for C₅₆H₅₄⁷⁹Br⁸¹BrNaO₇ (M + Na) 1021.211350, found 1021.211970. Anal. Calcd for C₅₆H₅₄O₇Br₂: C, 67.34; H, 5.45. Found: C, 67.40; H, 5.41.

74.84 (t'), 76.29 (s'), 78.42 (d'), 78.53 (d'), 81.04 (d'), 81.09 (s'), 86.69 (s'), 113.46 (d'), 113.81 (d'), 126.94 (d'), 127.25 (d'), 127.31 (d'), 127.79 (d'), 128.10 (d'), 128.29 (d'), 128.90 (d'), 129.61 (s'), 129.74 (d'), 129.93 (d'), 130.75 (s'), 138.74 (s'), 139.03 (s'), 144.12 (s'), 159.01 (s'), 159.33 (s'); exact mass (HR electrospray) m/z calcd for $C_{56}H_{54}NaO_7$ ($M + Na$) 861.376724, found 861.377150.

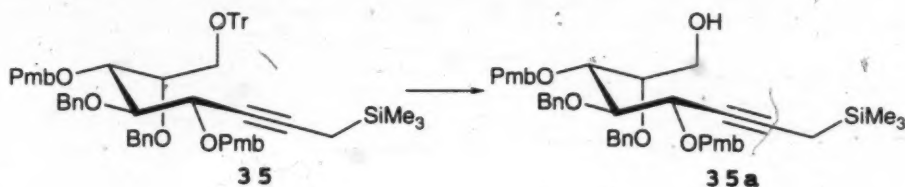
1,2,3-Trideoxy-4,6-bis-O-[(4-methoxyphenyl)methyl]-5,7-bis-O-(phenylmethyl)-1-(trimethylsilyl)-8-O-(triphenylmethyl)- β -gluco-oct-2-ynitol (35).



n -BuLi (2.5 M in hexane, 0.61 mL, 1.53 mmol) was added over 30 sec to a stirred and cooled ($-78\text{ }^{\circ}\text{C}$) solution of **34b** (1.15 g, 1.37 mmol) in THF (35 mL). Stirring at $-78\text{ }^{\circ}\text{C}$ was continued for 1 h, and then $\text{Me}_3\text{SiCH}_2\text{OSO}_2\text{CF}_3$ (0.35 mL, 1.75 mmol) and HMPA (1.0 mL, 5.75 mmol) were added, each in one portion. The cold bath was removed and stirring was continued for 8 h. The mixture was diluted with Et_2O (40 mL) and washed with brine (1 x 20 mL). The aqueous layer was extracted with Et_2O (2 x 20 mL) and the combined organic extracts were dried and evaporated. Flash chromatography of

the residue over silica gel (1.5 x 25 cm), using 1:9 EtOAc-hexane, gave **35** (1.04 g, 82%) as a pure (^1H NMR, 400 MHz), gummy solid: $[\alpha]_D = 19.4$ (c 1.17, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 2212 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 0.14 (s, 9 H), 1.63 (dd, $J = 16.4$, 2.2 Hz, 1 H), 1.66 (dd, $J = 16.4$, 2.2 Hz, 1 H), 3.21 (dd, $J = 10.3$, 4.7 Hz, 1 H), 3.60 (dd, $J = 10.3$, 2.2 Hz, 1 H), 3.75 (s, 3 H), 3.76 (s, 3 H), 3.80-3.85 (m, 1 H), 3.98 (dd, $J = 8.0$, 2.9 Hz, 1 H), 4.26 (d, $J = 11.5$ Hz, 1 H), 4.29 (dd, $J = 8.0$, 2.9 Hz, 1 H), 4.35 (d, $J = 10.5$ Hz, 1 H), 4.45-4.52 (m, 4 H), 4.69 (d, $J = 11.6$ Hz, 1 H), 4.77 (d, $J = 11.1$ Hz, 1 H), 4.91 (d, $J = 11.7$ Hz, 1 H), 6.65-6.69 (m, 2 H), 6.75-6.81 (m, 2 H), 6.82-6.86 (m, 2 H), 7.13-7.32 (m, 21 H), 7.41-7.50 (m, 6 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ -1.76 (q'), 7.43 (t'), 55.23 (q'), 62.80 (t'), 70.57 (t'), 71.88 (s'), 71.88 (d'), 74.33 (t'), 74.67 (t'), 75.98 (t'), 78.52 (d'), 78.79 (d'), 81.72 (d'), 86.65 (s'), 86.81 (s'), 113.41 (d'), 113.74 (d'), 126.88 (d'), 127.06 (d'), 127.15 (d'), 127.19 (d'), 127.74 (d'), 128.03 (d'), 128.22 (d'), 128.91 (d'), 129.69 (d'), 129.81 (d'), 130.20 (s'), 130.89 (s'), 138.88 (s'), 139.38 (s'), 144.19 (s'), 158.94 (s'), 159.17 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{60}\text{H}_{64}\text{NaO}_7\text{Si}$ (M + Na) 947.431903, found 947.432090. Anal. Calcd for $\text{C}_{60}\text{H}_{64}\text{O}_7\text{Si}$: C, 77.89; H, 6.97. Found: C, 77.81; H, 7.23.

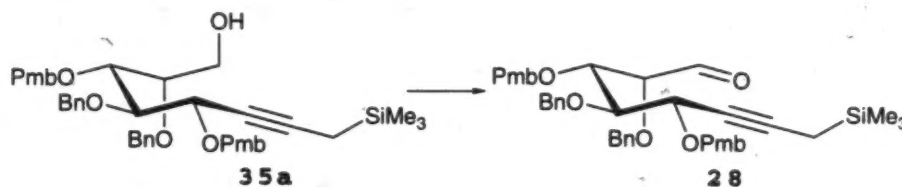
1,2,3-Trideoxy-4,6-bis-O-[(4-methoxyphenyl)methyl]-5,7-bis-O-(phenylmethyl)-1-(trimethylsilyl)-D-gluco-oct-2-ynitol (35a).



CSA (40.0 mg, 0.172 mmol) in MeOH (5 mL) was added in one portion to a stirred solution of **35** (1.17 g, 1.27 mmol) in CH₂Cl₂ (50 mL). Stirring was continued for 36 h, Et₃N (1 mL) was added, and the solution was evaporated. Flash chromatography of the residue over silica gel (1.5 x 25 cm), using 2:8 EtOAc-hexane, gave **35a** (0.82 g, 94%) as a pure (¹H NMR, 400 MHz) oil: [α]_D = 37.59 (c 3.20, CH₂Cl₂); FTIR (CH₂Cl₂ cast) 3492, 2212 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.13 (s, 9 H), 1.55 (d, *J* = 2.5 Hz, 2 H), 2.07 (dd, *J* = 7.5, 4.0 Hz, 1 H), 3.66-3.86 (m, including singlets at δ 3.78 and 3.79, 10 H), 4.15 (dd, *J* = 7.0, 4.0 Hz, 1 H), 4.28 (d, *J* = 11.7 Hz, 1 H), 4.43-4.49 (m, 3 H), 4.56 (d, *J* = 11.6 Hz, 1 H), 4.64 (s, 2 H), 4.77 (d, *J* = 11.2 Hz, 1 H), 4.93 (d, *J* = 11.3 Hz, 1 H), 6.78-6.84 (m, 4 H), 7.15-7.32 (m, 14 H); ¹³C NMR (CDCl₃, 100.6 MHz) δ -1.85 (q'), 7.36 (t'), 55.20 (q'), 60.33 (t'), 70.54 (t'), 71.22 (t'), 71.56 (d'), 74.59 (t'), 74.85 (t'), 75.43 (s'), 79.02 (d'), 79.04 (d'), 81.45 (d'), 86.97 (s'), 113.63 (s'), 113.72 (s'), 127.31 (d'), 127.46 (d'), 127.56 (d'), 127.97 (d'), 128.13 (d'), 128.35 (d'),

129.70 (d'), 129.97 (s'), 130.63 (s'), 138.25 (s'), 138.88 (s'), 159.15 (s'); exact mass (HR electrospray) m/z calcd for $C_{41}H_{50}NaO_7Si$ ($M + Na$) 705.322353, found 705.321500.

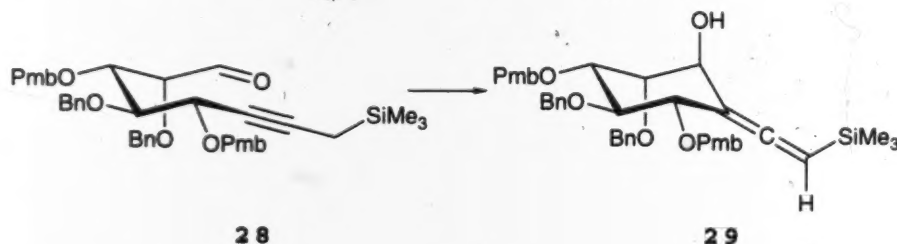
6,7,8-Trideoxy-3,5-bis-O-[(4-methoxyphenyl)methyl]-2,4-bis-O-(phenylmethyl)-8-(trimethylsilyl)-L-gulo-oct-6-ynose (28).



DMSO (0.43 mL, 6.06 mmol) was added dropwise to a stirred and cooled solution (-78°C) of $(\text{COCl})_2$ (0.40 mL, 4.58 mmol) in CH_2Cl_2 (30 mL). After 20 min, **35a** (1.02 g, 1.50 mmol) in CH_2Cl_2 (10 mL) was added by syringe over 1 min. Stirring was continued for 30 min at -78°C , and then Et_3N (1.72 mL, 12.3 mmol) was added. After a further 30 min, the cold bath was removed and stirring was continued for 6 h. The mixture was diluted with water (5 mL) and CH_2Cl_2 (20 mL), washed with brine (20 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 1:10 to 2:8 EtOAc-hexane, gave **28** (0.94 g, 92%) as a pure (^1H NMR, 400 MHz) oil: $[\alpha]_D = 33.38$ (c 1.33, CHCl_3); FTIR (CH_2Cl_2 , cast) 2212, 1733 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 0.14 (s, 9 H), 1.56 (d, $J = 2.5$ Hz, 2 H), 3.77 (s, 3 H), 3.78 (s, 3 H), 3.82 (dd, $J = 8.0, 4.5$ Hz, 1 H), 4.02 (dd, $J = 5.0,$

2.0 Hz, 1 H), 4.22-4.27 (m, 2 H), 4.40-4.58 (m, 6 H), 4.76 (d, $J = 11.7$ Hz, 1 H), 4.90 (d, $J = 11.5$ Hz, 1 H), 6.77-6.86 (m, 4 H), 7.15 (d, $J = 9.0$ Hz, 2 H), 7.18-7.34 (m, 12 H), 9.64 (d, $J = 2.0$ Hz, 1 H); ^{13}C NMR (CDCl_3 , 100.6 MHz) δ -1.81 (q'), 7.32 (t'), 55.25 (q'), 70.59 (t'), 71.33 (d'), 72.29 (t'), 74.23 (t'), 74.99 (t'), 75.23 (s'), 80.40 (d'), 81.47 (d'), 83.88 (d'), 86.98 (s'), 113.66 (d'), 113.78 (d'), 127.56 (d'), 127.79 (d'), 127.84 (d'), 128.26 (d'), 128.40 (d'), 129.77 (d'), 129.90 (d'), 129.99 (s'), 130.13 (s'), 137.52 (s'), 138.50 (s'), 159.28 (s'), 201.34 (d'); exact mass (HR electrospray) m/z calcd for $\text{C}_{41}\text{H}_{48}\text{NaO}_7\text{Si}$ ($M + \text{Na}$) 703.306703, found 703.306590.

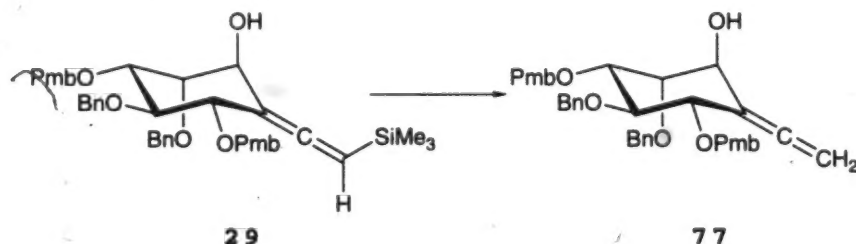
(R_a)-5-Deoxy-2,4-bis-*O*-[(4-methoxyphenyl)methyl]-1,3-bis-*O*-(phenylmethyl)-5-[(trimethylsilyl)ethenylidene]-*L*-chiro-inositol (**29**).



CSA (64 mg, 0.28 mmol) was added to a stirred solution of **28** (0.90 g, 1.32 mmol) in PhMe (200 mL). Stirring was continued for 2.5 h, Et_3N (2 mL) was added, and the solution was evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 2:8 EtOAc-hexane, gave **29**

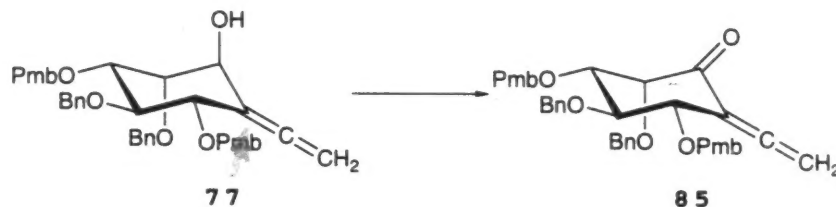
(0.82 g, 91%) as a pure (^1H NMR, 300 MHz), gummy solid: $[\alpha]_D = -0.504$ (c 4.96, CHCl_3); FTIR (CH_2Cl_2 cast) 3441, 1947 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.16 (s, 9 H), 1.97 (br s, 1 H), 3.74 (dd, $J = 6.6, 2.7$ Hz, 1 H), 3.80 (s, 6 H), 3.89 (dd, $J = 6.2, 2.9$ Hz, 1 H), 3.97 (dd, $J = 6.0, 6.0$ Hz, 1 H), 4.23 (dd, $J = 5.5, 2.6$ Hz, 1 H), 4.46 (d, $J = 11.2$ Hz, 1 H), 4.52 (d, $J = 11.5$ Hz, 1 H), 4.54-4.76 (m, 7 H), 5.35 (dd, $J = 2.7, 2.7$ Hz, 1 H), 6.78-6.87 (m, 4 H), 7.21-7.40 (m, 14 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ -0.84 (q'), 55.22 (q'), 68.42 (d'), 71.31 (t'), 72.13 (t'), 72.18 (t'), 73.81 (t'), 77.20 (d'), 77.97 (d'), 79.42 (d'), 86.43 (d'), 95.47 (s'), 113.62 (d'), 127.49 (d'), 127.81 (d'), 128.24 (d'), 128.28 (d'), 129.26 (d'), 129.41 (d'), 130.76 (s'), 130.79 (s'), 138.64 (s'), 159.03 (s'), 206.46 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{41}\text{H}_{48}\text{NaOSi}$ ($M + \text{Na}$) 703.306703, found 703.306710. Anal. Calcd for $\text{C}_{41}\text{H}_{48}\text{OSi}$: C, 72.32; H, 7.11. Found: C, 72.25; H, 7.11.

5-Deoxy-5-ethenylidene-2,4-bis-O-[(4-methoxyphenyl)methyl]-1,3-bis-O-(phenylmethyl)-L-chiro-inositol (77).



Powdered K_2CO_3 (~325 mesh, 0.880 g, 6.37 mmol) was added in one portion to a stirred solution of **29** (1.45 g, 2.13 mmol) in 3:1 MeOH-THF (280 mL), and the resulting mixture was refluxed for 4 h, cooled, diluted with Et_2O (50 mL), and filtered through a pad (2.5 x 2 cm) of flash chromatography silica gel, using Et_2O (50 mL) as a rinse. The combined filtrates were evaporated, and flash chromatography of the residue over silica gel (2 x 25 cm), using 3:7 EtOAc-hexane, gave **77** (1.12 g, 86%) as a pure (^1H NMR, 300 MHz) oil: $[\alpha]_D = 23.1$ (c 1.06, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3440, 1959 cm^{-1} ; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.14 (br s, 1 H), 3.76 (dd, $J = 6.1$, 2.9 Hz, 1 H), 3.80 (s, 6 H), 3.88 (dd, $J = 6.9$, 2.8 Hz, 1 H), 3.98 (dd, $J = 6.6$, 6.6 Hz 1 H), 4.25 (ddd, $J = 6.2$, 2.7, 2.7 Hz, 1 H), 4.49 (d, $J = 10.7$ Hz, 1 H), 4.52-4.78 (m, 8 H), 4.97-5.11 (m, 2 H), 6.78-6.87 (m, 4 H), 7.20-7.41 (m, 14 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 55.24 (q'), 68.93 (d'), 71.85 (t'), 72.26 (t'), 72.35 (t'), 74.26 (t'), 77.53 (d'), 78.46 (t'), 78.95 (d'), 80.04 (d'), 101.83 (s'), 113.66 (d'), 127.52 (d'), 127.69 (d'), 127.83 (d'), 128.29 (d'), 129.41 (d'), 129.49 (d'), 130.55 (s'), 130.78 (s'), 138.51 (s'), 138.77 (s'), 159.08 (s'), 205.81 (s'); exact mass (HR electrospray) m/z calcd for $C_{38}H_{40}NaO_7$ (M + Na) 631.267174, found 631.266900.

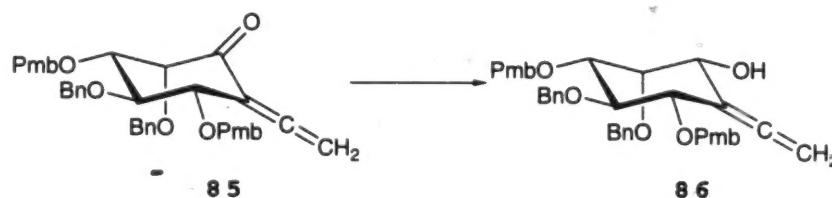
(3*S*,4*R*,5*S*,6*S*)-2-Ethenylidene-3,5-bis[(4-methoxyphenyl)methoxy]-4,6-bis-(phenylmethoxy)cyclohexanone (**85**).



A solution of **77** (296.7 mg, 0.488 mmol) in CH_2Cl_2 (6 mL) was added to a stirred suspension of Dess-Martin periodinane (289.6 mg, 0.693 mmol) in CH_2Cl_2 (12 mL). The mixture was stirred for 30 min, diluted with Et_2O (18 mL), and poured into saturated aqueous NaHCO_3 (18 mL) containing $\text{Na}_2\text{S}_2\text{O}_3$ (4.5 g). The mixture was stirred for 5 min. Et_2O (20 mL) was added, and the layers were separated. The Et_2O layer was washed with saturated aqueous NaHCO_3 (20 mL), water (20 mL) and brine (10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1 x 25 cm), using 3:7 EtOAc -hexane, gave **85** (248.3 mg, 84%) as a pure (^1H NMR, 400 MHz), gummy solid: $[\alpha]_D = -13.7$ (c 1.30, acetone); FTIR (CH_2Cl_2 cast) 1960, 1708 cm^{-1} ; ^1H NMR (CD_2Cl_2 , 400 MHz) δ 3.77 (s, 3 H), 3.78 (s, 3 H), 3.87 (dd, $J = 5.6, 2.3$ Hz, 1 H), 3.98 (dd, $J = 4.8, 4.8$ Hz, 1 H), 4.27 (d, $J = 2.5$ Hz, 1 H), 4.38 (ddd, $J = 5.6, 4.1, 4.1$ Hz, 1 H), 4.45-4.57 (m, 6 H), 4.66 (d, $J = 11.2$ Hz, 1 H), 4.86 (d, $J = 11.9$ Hz, 1 H), 5.41 (dd, $J = 14.9, 4.0$ Hz, 1 H), 5.43 (dd, $J = 14.9, 4.0$ Hz, 1 H), 6.80-6.91 (m, 4 H), 7.17-7.41 (m, 14 H); ^{13}C NMR (CDCl_3 ,

75.5 MHz) δ 55.30 (q'), 71.99 (t'), 72.27 (t'), 72.57 (t'), 72.63 (t'), 76.74 (d'), 77.39 (d'), 81.24 (d'), 81.82 (d'), 82.06 (t'), 104.26 (s'), 113.71 (d'), 113.80 (d'), 127.76 (d'), 127.82 (d'), 127.87 (d'), 127.89 (d'), 128.40 (d'), 128.47 (d'), 129.58 (d'), 129.62 (d'), 129.93 (s'), 130.06 (s'), 137.84 (s'), 159.26 (s'), 159.36 (s'), 194.61 (s'), 211.22 (s'); exact mass (HR electrospray) m/z calcd for $C_{38}H_{38}NaO_7$ ($M + Na$) 629.251524, found 629.251915.

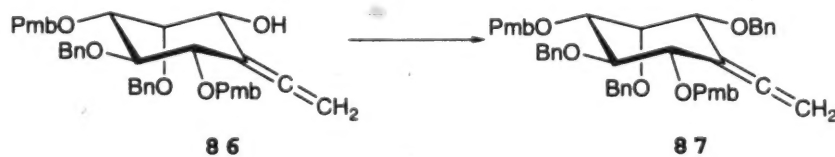
4-Deoxy-4-ethenylidene-1,5-bis-O-[(4-methoxyphenyl)methyl]-2,6-bis-O-(phenylmethyl)-D-myo-inositol (86).



$CeCl_3 \cdot 7H_2O$ (0.42 g, 1.13 mmol) was added in one portion to a stirred solution of **85** (0.63 g, 1.04 mmol) in 1:10 THF-MeOH (126 mL). After 10 min, the mixture was cooled to $-78^\circ C$, and $NaBH_4$ (42.8 mg, 1.13 mmol) was added. Stirring was continued at $-78^\circ C$ for 1 h, and then at $0^\circ C$ (ice bath) for 4 h. The reaction was quenched with saturated aqueous NH_4Cl (25 mL), and the mixture was diluted with water (25 mL), evaporated, and extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with brine (1 x 20 mL), dried, and evaporated. Flash chromatography of the residue

over silica gel (1.5 x 20 cm), using 3:7 EtOAc-hexane, gave **86** (0.58 g, 92%), as a pure (^1H NMR, 300 MHz), gummy solid: $[\alpha]_{\text{D}} = 56.3$ (c 2.05, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3479, 1970 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 2.66 (d, $J = 11.0$ Hz, 1 H), 3.53 (dd, $J = 8.2, 2.5$ Hz, 1 H), 3.80 (s, 3 H), 3.81 (s, 3 H), 3.89-3.96 (m, 2 H), 4.00 (dd, $J = 8.0, 8.0$ Hz, 1 H), 4.06 (ddd, $J = 10.8, 3.0, 3.0$ Hz, 1 H), 4.49 (d, $J = 10.9$ Hz, 1 H), 4.57-4.80 (m, 5 H), 4.83 (d, $J = 11.0$ Hz, 1 H), 4.98 (d, $J = 11.8$ Hz, 1 H), 5.11-5.22 (m, 2 H), 6.78-6.86 (m, 4 H), 7.22-7.41 (m, 14 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 55.26 (q'), 67.93 (d'), 72.40 (t'), 72.92 (t'), 73.76 (t'), 75.06 (t'), 77.44 (d'), 78.31 (d'), 79.83 (d'), 81.19 (d'), 81.58 (t'), 103.77 (s'), 113.73 (d'), 113.80 (d'), 127.47 (d'), 127.49 (d'), 127.54 (d'), 127.94 (d'), 128.30 (d'), 128.34 (d'), 129.37 (d'), 129.77 (d'), 130.27 (s'), 130.39 (s'), 138.82 (s'), 138.88 (s'), 159.24 (s'), 203.21 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{38}\text{H}_{40}\text{NaO}_7$ ($M + \text{Na}$) 631.267174, found 631.267670.

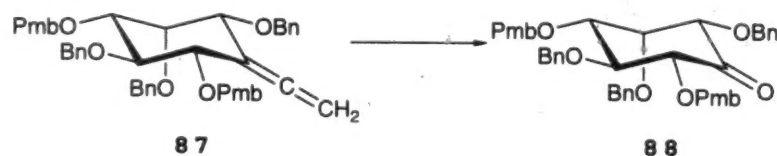
4-Deoxy-4-ethenylidene-1,5-bis-O-[(4-methoxyphenyl)methyl]-2,3,6-tris-O-(phenylmethyl)-D-myo-inositol (87).



NaH (80% dispersion in oil, 34.2 mg, 1.14 mmol) was

added in one portion to a stirred and cooled (0 °C) solution of **86** (0.580 g, 0.954 mmol) in THF (40 mL). After 30 min, BnBr (0.14 mL, 1.14 mmol) was added neat in one portion, the cold bath was removed, and the mixture was stirred for 1 h and then refluxed for 24 h. The resulting mixture was cooled (0 °C) and quenched with MeOH (5 mL), diluted with brine (10 mL), and extracted with Et₂O (3 x 20 mL). The combined organic extracts were washed with brine (1 x 20 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 2:8 EtOAc-hexane, gave **87** (0.580 g, 87%) as a pure (¹H NMR, 300 MHz), white solid: mp 100-101 °C; [α]_D = 1.50 (c 1.60, CHCl₃); FTIR (CH₂Cl₂ cast) 1965 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 3.29 (dd, *J* = 9.5, 2.5 Hz, 1 H), 3.69-3.74 (m, 1 H), 3.75-3.84 (m, including singlets at δ 3.80 and 3.81, 7 H), 3.97-4.06 (m, 2 H), 4.44 (d, *J* = 11.9 Hz, 1 H), 4.50-4.59 (m, 3 H), 4.75-4.96 (m, 6 H), 5.14-5.30 (m, 2 H), 6.78-6.87 (m, 4 H), 7.18-7.43 (m, 19 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 55.31 (q'), 71.89 (t'), 72.21 (t'), 73.09 (t'), 73.35 (t'), 75.88 (t'), 76.11 (d'), 76.54 (d'), 78.09 (d'), 80.10 (d'), 81.76 (t'), 83.08 (d'), 101.25 (s'), 113.75 (d'), 127.06 (d'), 127.41 (d'), 127.44 (d'), 127.59 (d'), 127.81 (d'), 128.00 (d'), 128.10 (d'), 128.25 (d'), 128.36 (d'), 129.30 (d'), 129.79 (d'), 130.49 (s'), 130.69 (s'), 138.31 (s'), 139.26 (s'), 139.37 (s'), 159.16 (s'), 159.27 (s'), 202.75 (s'); exact mass (HR electrospray) *m/z* calcd for C₄₅H₄₆NaO₇ (M + Na) 721.314124, found 721.316612.

1,5-Bis-O-[(4-methoxyphenyl)methyl]-2,3,6-tris-O-(phenylmethyl)-D-*epi*-4-inosose (88).



The apparatus described⁶⁵ by Rubin was used for this experiment. A cold (-78 °C), saturated solution of ozone in CH₂Cl₂ (21.5 mL) was transferred to a stirred and cooled (-78 °C) solution of **87** (188.1 mg, 0.269 mmol) and pyridine (3.2 mL) in CH₂Cl₂ (20 mL). The mixture was stirred for 30 min, and then evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 2:8 EtOAc-hexane, gave **88** [109.1 mg, 80% (after correction for recovered starting material (50.5 mg, 27%)] as a pure (¹H NMR, 400 MHz), white solid: mp 150-151 °C; [α]_D = 24.1 (c 1.12, CHCl₃); FTIR (CH₂Cl₂ cast) 1740 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 3.68 (dd, *J* = 9.4, 2.1 Hz, 1 H), 3.80 (s, 3 H), 3.82 (s, 3 H), 3.93-3.99 (m, 2 H), 4.10 (dd, *J* = 2.1, 2.1 Hz, 1 H), 4.19 (dd, *J* = 9.4, 9.4 Hz, 1 H), 4.47 (d, *J* = 11.9 Hz, 1 H), 4.50-4.59 (m, 3 H), 4.78-4.91 (m, 6 H), 6.81-6.88 (m, 4 H), 7.17-7.41 (m, 19 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 55.29 (q'), 55.30 (q'), 72.22 (t'), 72.46 (t'), 73.20 (t'), 73.66 (t'), 75.76 (d'), 75.92 (t'), 79.78 (d'), 81.37 (d'), 82.58 (d'), 83.70 (d'), 113.82 (d'), 127.42 (d'), 127.57 (d'), 127.81 (d'), 127.97 (d'), 128.03 (d'), 128.13 (d'), 128.29 (d'), 128.51 (d'), 129.36 (d'), 129.84 (s'), 129.90 (d'), 130.10 (s'), 137.40 (s').

138.26 (s'), 138.75 (s'), 159.31 (s'), 159.41 (s'), 201.74 (s'); exact mass (HR electrospray) m/z calcd for $C_{43}H_{44}NaO_8$ (M + Na) 711.293389, found 711.293620.

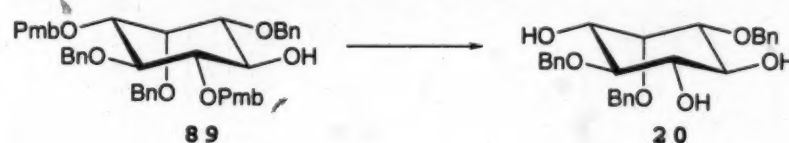
1,5-Bis-O-[(4-methoxyphenyl)methyl]-2,3,6-tris-O-(phenylmethyl)-D-myo-inositol (89).



A solution of $n\text{-Bu}_2\text{SnCl}_2$ (279 mg, 0.918 mmol) in PhMe (5 mL) was added to a stirred solution of $n\text{-Bu}_2\text{SnH}_2$ (216 mg, 0.918 mmol) in PhMe (5 mL), and the mixture was stirred at room temperature for 15 min. A solution of **88** (63.3 mg, 0.0920 mmol) in PhMe (6 mL) was added, and the resulting solution was refluxed for 24 h, and then cooled to room temperature. MeOH (2 mL) was added, and the solvents were evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 2:8 EtOAc-hexane, gave **89** (56.2 mg, 88%) as a pure (^1H NMR, 300 MHz), gummy solid: $[\alpha]_D = 8.00$ (c 2.26, CHCl_3); FTIR (CH_2Cl_2 cast) 3473 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 2.40 (br s, 1 H), 3.17 (dd, $J = 9.8, 2.2$ Hz, 1 H), 3.35 (dd, $J = 9.0, 9.0$ Hz, 1 H), 3.36 (dd, $J = 9.0, 2.4$ Hz, 1 H), 3.79 (s, 3 H), 3.81 (s, 3 H), 4.00 (dd, $J = 2.2, 2.2$ Hz, 1 H), 4.02 (dd, $J = 9.6, 9.6$ Hz, 1 H), 4.15 (dd, $J = 9.6, 9.6$ Hz, 1 H), 4.52-4.63 (m, 4 H), 4.73-4.94 (m, 6 H), 6.80-6.90 (m, 4 H), 7.18-7.42 (m, 19 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ

55.32 (q'), 72.33 (t'), 72.56 (t'), 72.96 (d'), 73.82 (d'), 74.08 (t'), 75.04 (t'), 75.75 (t'), 80.15 (d'), 80.92 (d'), 81.47 (d'), 83.25 (d'), 113.84 (d'), 113.88 (d'), 127.37 (d'), 127.51 (d'), 127.75 (d'), 127.85 (d'), 128.01 (d'), 128.18 (d'), 128.34 (d'), 128.52 (d'), 129.29 (d'), 129.56 (d'), 130.49 (s'), 131.12 (s'), 138.07 (s'), 138.95 (s'), 139.01 (s'), 159.22 (s'), 159.26 (s'); exact mass (HR electrospray) m/z calcd for $C_{43}H_{46}NaO_8$ 713.309039, found 713.309230.

2,3,6-Tris-O-(phenylmethyl)-D-myo-inositol (20).



DDQ (55.9 mg, 0.246 mmol) was added in one portion to a stirred solution of **89** (51.5 mg, 0.0746 mmol) in CH_2Cl_2 (20 mL) and water (1 mL). Stirring was continued for 4 h, and the solution was then washed with saturated aqueous $NaHCO_3$ (10 mL), water (10 mL) and brine (10 mL), dried, evaporated. Flash chromatography of the residue over silica gel (1 x 10 cm), using 1:1 EtOAc-hexane, gave **20** (23.5 mg, 70%) as a pure (^1H NMR, 400 MHz), white solid: mp 122-123 °C; $[\alpha]_D = 10.3$ (c 1.73, $CHCl_3$); Lit.⁶⁶ mp 117-119 °C; $[\alpha]_D^{16} = 15.5$ (c 1, $CHCl_3$); Lit.⁶⁷ mp 117-119 °C; $[\alpha]_D = 12.4$ (c = 0.8, $CHCl_3$); Lit.⁶⁸ mp 121-123 °C; $[\alpha]_D^{25} = 10$ (c 1, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3439 cm^{-1} ; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.37 (br d, $J = 6.1$

Hz, 1 H), 2.68 (br s, 2 H), 3.27 (dd, $J = 9.8, 2.4$ Hz, 1 H), 3.47 (dd, $J = 9.1, 9.1$ Hz, 1 H), 3.52 (br d, $J = 9.0$ Hz, 1 H), 3.68 (dd, $J = 9.3, 9.3$ Hz, 1 H), 4.01 (dd, $J = 9.4, 9.4$ Hz, 1 H), 4.08 (dd, $J = 2.5, 2.5$ Hz, 1 H), 4.58 (d, $J = 11.6$ Hz, 1 H), 4.69 (d, $J = 11.6$ Hz, 1 H), 4.72 (d, $J = 11.4$ Hz, 1 H), 4.84 (d, $J = 11.3$ Hz, 1 H), 4.88 (d, $J = 11.3$ Hz, 1 H), 4.93 (d, $J = 11.4$ Hz, 1 H), 7.28-7.40 (m, 15 H); ^{13}C NMR (CDCl_3 , 75.5 Hz) δ 72.58 (t'), 72.59 (d'), 72.61 (d'), 74.80 (t'), 74.89 (d') 75.09 (t'), 76.43 (d'), 80.28 (d'), 81.77 (d'), 127.79 (d'), 127.87 (d'), 127.93 (d'), 128.11 (d'), 128.47 (d'), 128.61 (d'), 128.64 (d'), 137.72 (s'), 138.54 (s'), 138.62 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{27}\text{H}_{30}\text{NaO}_6$ ($M + \text{Na}$) 473.194009, found 473.194360.

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Part 2

**Synthetic Studies on the Farnesyl Transferase
Inhibitors CP-225,917 and CP-263,114.**

Introduction

The closely related natural products CP-225,917 (**1**) and CP-263,114 (**2**) were isolated recently from an unidentified fungus by a Pfizer research group.¹ The compounds are inhibitors of ras-farnesyl protein transferase² and,

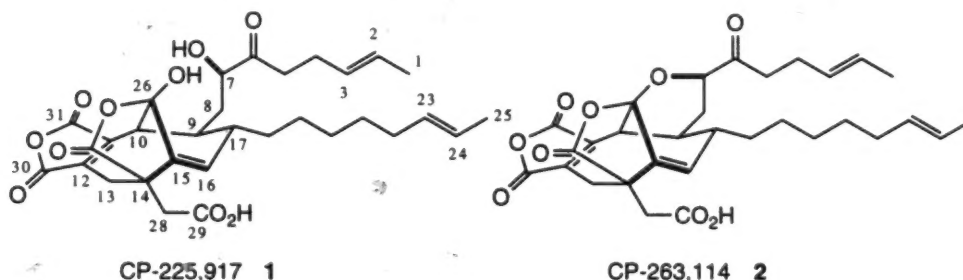


Figure 1 Structures of **1** and **2**

therefore, they constitute intriguing lead compounds for the development of drugs for cancer chemotherapy.³ Structurally, they are related to the nonadride family of natural products⁴ in that they contain a nine-membered ring fused to a maleic anhydride moiety. They are presumed to be biosynthesized^{1,2} in a comparable way to the nonadrides. Interestingly, **1** and **2** also contain a bridgehead olefin. Synthetic work on these compounds provides opportunities for contributions to Biology

and Medicine, as well as to Chemistry.

Several early and interesting model studies directed to the synthesis of CP-225,917 (1) and CP-263,114 (2) have been reported by Nicolaou,^{5,6} Davies,⁷ Clive,⁸ Armstrong,⁹ Danishefsky,¹⁰ Fukuyama,¹¹ and Shair.¹²

Two topics are relevant in the review section for my work on the synthesis of CP-225,917 (1) and CP-263,114 (2): the biological basis of the importance of the compounds, and recent synthetic studies related to 1 and 2.

1. Biological activity of CP-225,917 and CP-263,114

The idea of inhibiting the action of the enzyme farnesyl transferase is an important recent step in the search for new approaches to the chemotherapy of cancer. The fungal metabolites 1 and 2 are inhibitors of this enzyme, and so the compounds serve as lead structures for the design of other inhibitors. The development of such inhibitors holds great promise for the discovery of a new commercial anticancer drug. The role of farnesyl transferase, and the unusual opportunity it provides for chemical intervention as a cure for cancer, is described in the following paragraphs.

Cell-growth is a carefully regulated process; occasionally, however, the mechanisms that control cell proliferation fail.

The proteins responsible for control of cell-growth are encoded by four classes of proto-oncogenes: growth factors (Class I proto-oncogenes), growth factor receptors (Class II

proto-oncogenes), intracellular signal transducers (Class III proto-oncogenes), and nuclear transcription factors (Class IV proto-oncogenes).¹³ Of all classes of proto-oncogenes, intracellular signal transducers (Class III) is the largest,¹³ and comprises the ras genes [Harvey (Ha), Kirsten (Ki), and N-ras].¹⁴ The ras gene products, a family of 21-kDa proteins, called p21 or Ras,^{14,15} play key roles in cellular processes such as proliferation and differentiation, and are closely associated with 30% of all human cancers.¹⁶

Alterations in the function of ras gene products (Ras), particularly Ki-Ras and N-Ras, are found in many different tumors, including carcinomas of the colon, pancreas, and lung, in neurofibrosarcomas, and in some leukemias.¹⁴

The transformation of the normal ras proto-oncogene into a ras oncogene can be triggered by carcinogens or oncogenic viruses; the ras oncogene then codes for the synthesis of a mutant oncogenic Ras.¹⁵ The most common mutation of the ras genes in human cancer cells produces Ras that lack GTPase activity,¹⁷ the fundamental process that turns the cell-growth mechanism off - by converting an active GTP-Ras complex into an inactive GDP-Ras complex. The membrane-bound mutant Ras, if permanently activated, continuously generates proliferation signals,¹⁴ thus leading to cancer.

Ras is synthesized as a biologically inactive precursor protein and is found in the soluble fraction (cytoplasm) of cells.¹⁸ Several post-translational modifications are required at the carboxy-terminal end of Ras before it becomes

a biologically active protein that is then localized in the plasma membrane.

Ras has a four residue 'CaaX' box (C is cysteine, a is an aliphatic amino acid, and X is an unspecified amino acid). Ras first undergoes farnesylation (attachment of a C₁₅-lipid chain to the C of the CaaX box).³ Farnesyl protein transferase (FPTase) catalyzes this reaction, using farnesyl diphosphate and the CaaX box as co-substrates.¹⁸

Farnesylation is essential to Ras function in yeast and mammalian cells.¹⁹ The original interest in FPTase inhibitors (FTIs) as cancer chemotherapeutics was derived from the idea that inhibition of this enzyme would in turn inhibit Ras function.

FTIs inhibit the growth of the majority of human tumor cells in culture. In a variety of animal systems, including v-H-ras transgenic mice and xenograft models, FTIs inhibit tumor growth, causing complete regression in some murine models.^{20,21} However, it is not clear that the key defarnesylated target protein is Ras. There is evidence that other members of the Ras family such as Rho are also affected and may be important in mediating the anti tumor activities of Ras farnesylation inhibitors.

Remarkably, even though FTIs affect the processing of wild-type Ras protein, the drug has little discernible toxicity in animals at doses that have major anti-tumor effects.²¹ There has been some speculation as to why normal cells are immune to the action of FPTase inhibitors, but the

precise reasons for the selectivity for tumor cells versus normal cells have not been established.

Numerous inhibitors of FPTase have been identified by modification of the substrates (farnesyl diphosphate and CaaX tetrapeptides) and by random screening of natural products, chemical collections, and combinatorial libraries.¹⁸ Two of these compounds, being developed by Schering-Plough and Janssen Pharmaceutical, are currently being evaluated in patients as anticancer agents.²²

CP-225,917 is a Ras protein farnesyl transferase inhibitor (IC_{50} 6.0 μM), although its mode of action, and what features confer inhibitory properties are unknown. One might speculate, however, that the anhydride substructure serves as a prodrug that is converted into a dicarboxylic acid on hydrolysis. In this regard it is noteworthy that the chaetomelic acids²³ (which are alkyl derivatives of maleic acid) are also inhibitors of farnesyl transferase. The hydrocarbon appendages may mimic the farnesyl unit that becomes attached to the Ras protein, and suggests that the hydrocarbon chains of CP-225,917 may be important, although those present in the natural product may not be optimal. No synthetic route to CP-225,917 is presently available, and so little advantage can be taken of the knowledge that the peculiar structure represented by CP-225,917 is a farnesyl transferase inhibitor.² Current synthetic work, described in the following section, therefore, may provide the tools necessary for the design of novel anticancer drugs based on

the properties and features of the natural products **1** and **2**.

2. Recent synthesis studies related to CP-225,917 and CP-263,142

No synthetic route to CP-225,917 is available, but several groups including our group have reported model studies needed before embarking on a total synthesis.

Inspection of the structures of **1** and **2** reveals that the basic carbon skeleton can be reduced to model system **3**, which contains the key and challenging bicyclic core as well as anchor groups for elaborating the remaining functionalities and side chains.

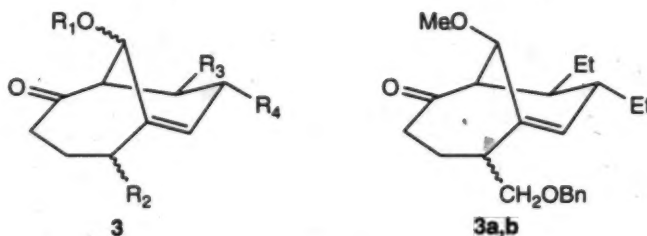


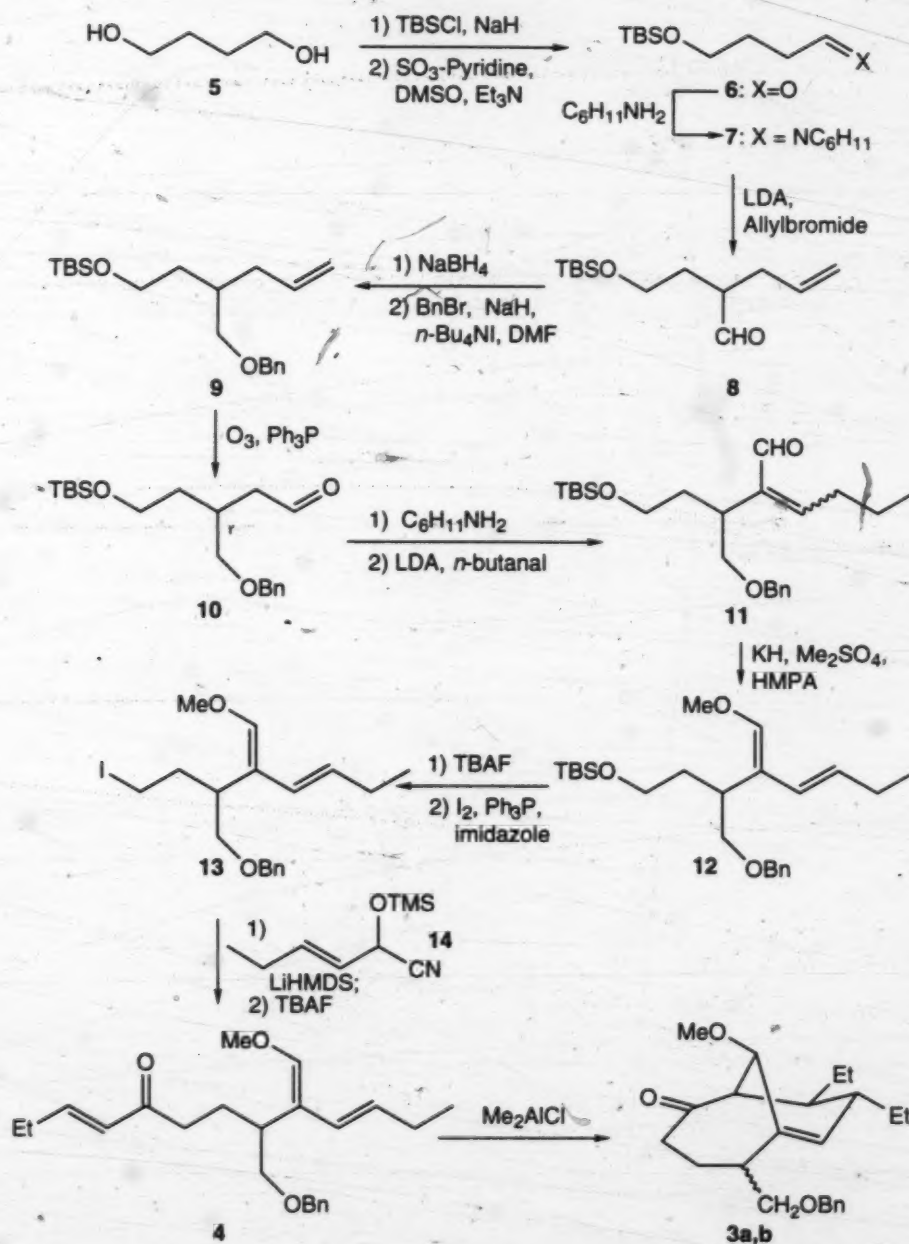
Figure 2 Structure of **3** and **3a,b**

There have been several reports describing approaches to the bicyclic core.

a. Nicolaou's Approaches

Nicolaou and his colleagues⁵ applied a Diels-Alder reaction to prepare **3a,b**. Analysis of structures **3a,b** leads to the open-chain triene **4** as a potential precursor (Scheme 1). The synthesis of **4** started from 1,4-butanediol (**5**).

Scheme 1



Monosilylation of **5**, followed by oxidization, gave aldehyde **6**. Alkylation of **6**, via its *N*-cyclohexylimine derivative **7**, with allyl bromide furnished **8**. After reduction of **8** and

benzylation, the resulting terminal olefin **9** was cleaved by ozonolysis to give aldehyde **10**. Formation of the imine of **10**, generation of the anion, and condensation with *n*-butanal afforded aldehyde **11** as a mixture of isomers (*E*:*Z* ca. 1:1). Methylation of **11** with Me_2SO_4 in the presence of KH and HMPA proceeded to afford diene **12** as a single geometrical isomer. Desilylation of **12** and iodination of the corresponding alcohol gave the iodide **13**. Reaction of **13** with the lithio derivative of the TMS-protected cyanohydrin **14**, followed by exposure to TBAF, led to the key triene **4**.

Triene **4** underwent intramolecular Diels-Alder reaction in the presence of Me_2AlCl in CH_2Cl_2 at -10°C . Two cycloadducts (**3a,b**) (stereochemistry unassigned) were obtained in 66% and 20% yield, respectively. The synthesis of **3a,b** defines a possible strategy for the total synthesis of **1** and **2**.

Nicolaou's preliminary studies also included compound **15** as a model target (see Figure 3). His group reported⁶ a

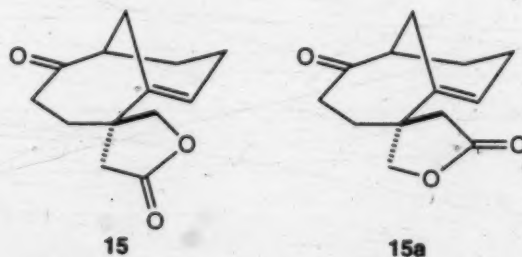


Figure 3 Structure of **15** and **15a**

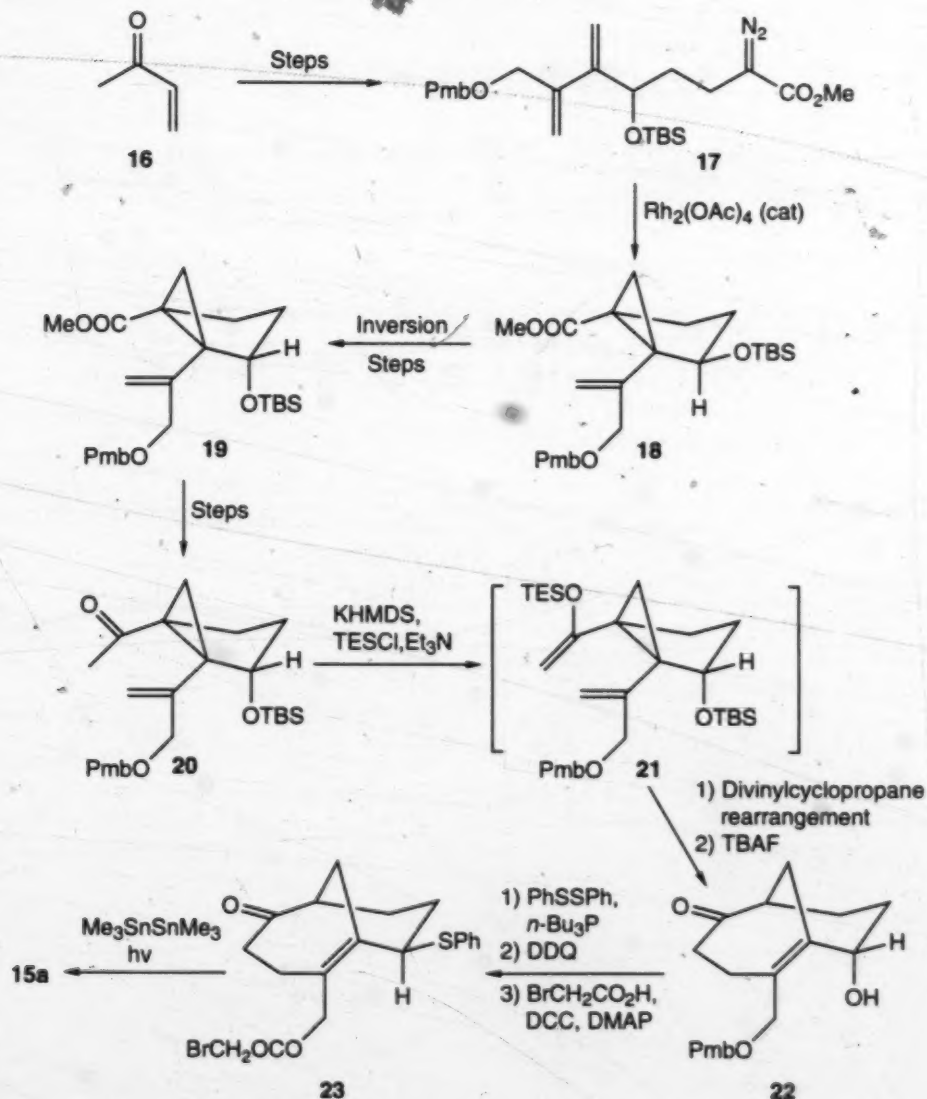
series of reactions (Scheme 2) which resulted in the

construction of **15a**, a substance that has the opposite stereochemistry at the quaternary center to that shown in **15**.

The synthetic route to **15a** is summarized in Scheme 2.

Methyl vinyl ketone (**16**) was transformed into the diazo ester

Scheme 2



17 in several steps.²⁴ Treatment of **17** with a catalytic

amount of $\text{Rh}_2(\text{OAc})_4$ led predominantly to vinylcyclopropane **18**, together with some C(2) diastereoisomer **19**. The configuration of **18** was inverted to **19** in several routine steps, including Mitsunobu inversion.²⁵ The desired product **20** was then reached by a series of functional group manipulations,²⁶ and the derived silyl enol ether **21** was then generated. This compound underwent a divinylcyclopropane rearrangement to give, after removal of both silyl groups, alcohol **22**. Replacement of the hydroxyl by a PhS group, with inversion, removal of the PMB unit, and protection of the liberated hydroxyl as an α -bromoacetate, furnished compound **23**.

Exposure of **23** to $\text{Me}_3\text{SnSnMe}_3$ and irradiation (hv) led to lactone **15a** by means of radical intermediates and ring closure with concomitant expulsion of sulfenyl radical. This last operation served to generate simultaneously the required quaternary center (albeit with the opposite stereochemistry to that of **15**) and the bridgehead olefin, two of the challenging structural elements in **1** and **2**.

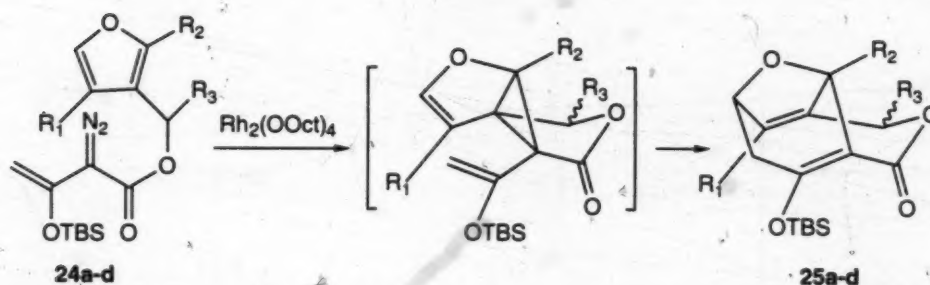
b. Davies' Approach

Motivated by the unusual structure of **1** and **2**, Davies⁷ explored a route for the synthesis of [4.3.1]-bicyclic compounds using tandem cyclopropanation/Cope rearrangement (Scheme 3).

Rhodium(II) octanoate-catalyzed decomposition of **24a** (for values of a-d, see Table 1) resulted in formation of the

tricyclic product **25a**. Further studies were carried out on

Scheme 3



more elaborate furan systems. The results are listed in Table 1.

Table 1 Synthesis of [4.3.1]-bicyclic compounds

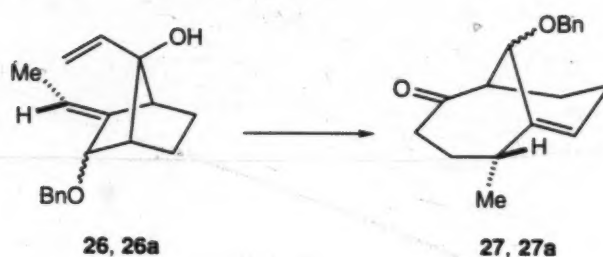
	R_1	R_2	R_3	yield %
a	H	H	H	83
b	H	Me	H	29
c	CH_2Bn	H	H	66
d	H	H	Et	48

These experiments illustrated a rapid method for construction of fused [4.3.1]-bicyclic systems.

c. Clive's Approach

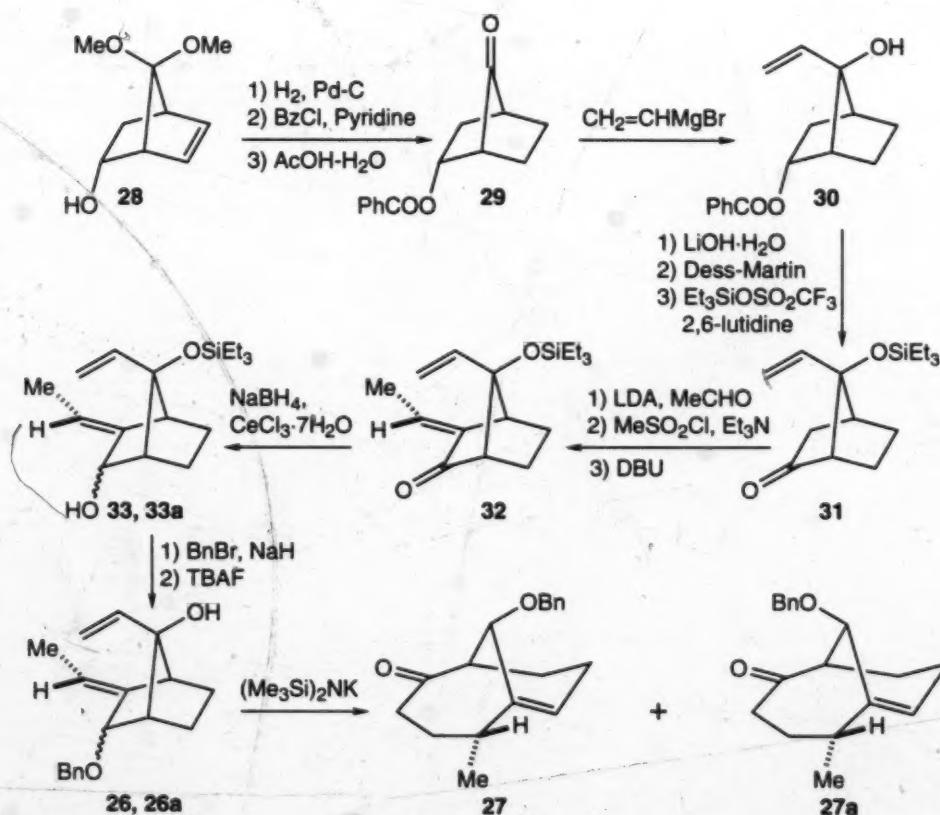
Immediately after the appearance of Nicolaou's first model study, our group published a route to compounds **27** and **27a**.

Scheme 4



The approach was based on the idea that anionic oxy-Cope rearrangement of **26, 26a** should lead to ketones **27, 27a**, which

Scheme 5



have a number of features that are appropriate for further

elaboration to substances that closely resemble **1** and **2**.

The model study began with the known norbornene **28**²⁷ (Scheme 5). The double bond was first saturated, the resulting alcohol was benzoylated, and the acetal group was hydrolyzed to give ketone **29**. Treatment of **29** with vinylmagnesium bromide afforded a mixture of tertiary alcohols, with the desired isomer **30** being the major (5:1) product. After hydrolysis of the benzoyl group, oxidation of the resulting diol, and protection of the tertiary hydroxyl, gave keto alcohol **31**.

The remainder of the hexa-1,5-diene subunit required for the anionic oxy-Cope rearrangement was assembled by a short sequence: aldol condensation, mesylation and base-induced elimination. Reduction of the major enone isomer (**32**) gave a 1:1 mixture of *endo*- and *exo*-alcohols (**33**, **33a**), which were separated and individually protected by benzylation.

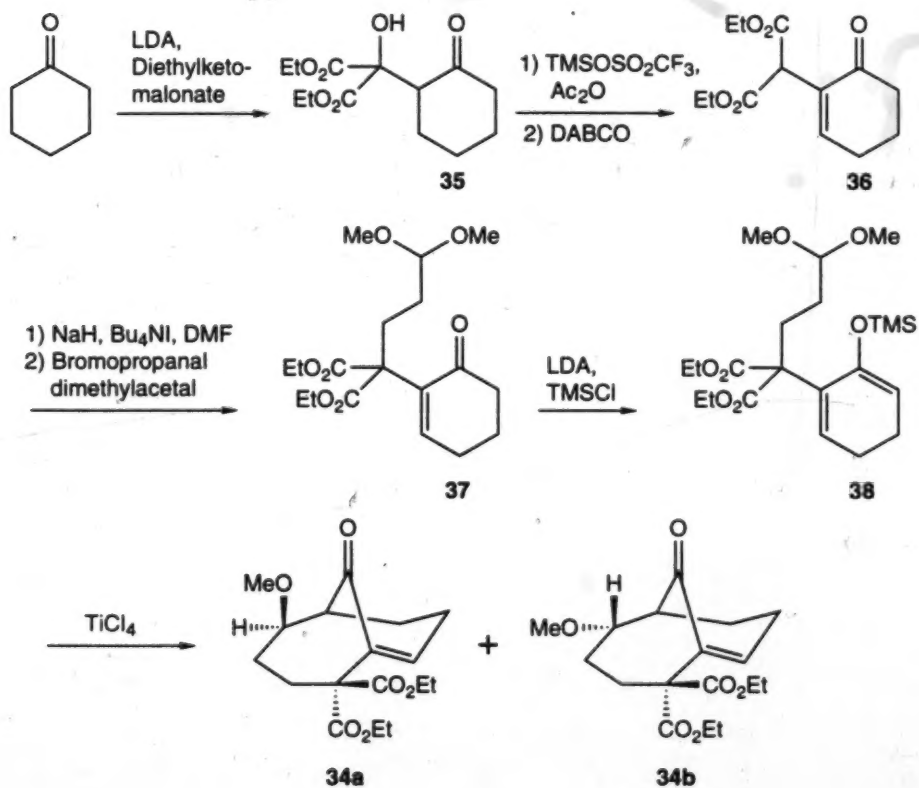
After desilylation, the individual alcohols **26** and **26a** were subjected to anionic oxy-Cope rearrangement [$(\text{Me}_3\text{Si})_2\text{NK}$, PhMe, 100 °C, ca. 20 h]. The *endo*-benzyl ether **26** gave **27**, and the *exo* isomer **26a** gave **27a**. Formation of both of these ketones serves as an initial test of the plan to reach **1** and **2**.

d. Armstrong's Approach

Armstrong's group⁹ has described a short (6 steps) synthesis of the bicyclo[4.3.1]decenones **34a** and **34b** from cyclohexanone (Scheme 6). The reaction of the lithium

enolate of cyclohexanone with diethyl ketomalonate gave **35**. Conversion of **35** into **36** was achieved by acetylation, followed by treatment with DABCO to effect acetate elimination and alkene isomerization. Regioselective alkylation with 3-bromopropanal dimethylacetal furnished **37**.

Scheme 6

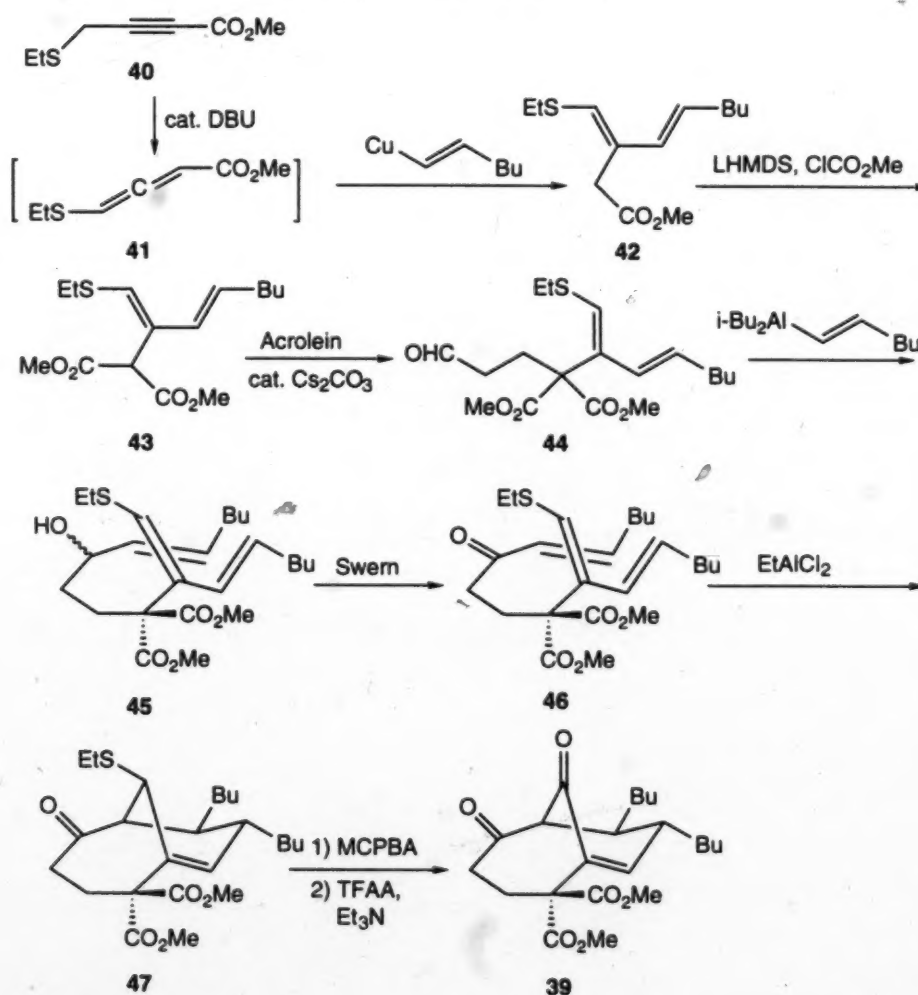


Conversion of **37** into the trimethylsilyl enol ether **38** then set the stage for the key ring-closure step. Treatment of **38** with TiCl₄ in CH₂Cl₂, resulted in an intramolecular Mukaiyama aldol reaction, and provided the desired bicyclic products **34a** and **34b**.

e. Fukuyama's Approach

Fukuyama's group¹¹ used an approach that involves an intramolecular Diels-Alder reaction to form the bicyclic model **47**, which was modified so as to generate **39**, a compound that possess most of the functional groups and the stereogenic centers required for the total synthesis of **1** and **2**.

Scheme 7



The starting point for the synthesis (Scheme 7) involved isomerization of methyl 4-ethylthio-2-butyrate **40** by DBU to provide an intermediate allenic ester **41**. The addition of 1-hexenylcopper to **41** gave (*E,E*)-diene **42** with high stereoselectivity. After introducing the second methoxycarbonyl group, the resulting malonate **43** was subjected to Michael addition to acrolein so as to afford aldehyde **44**. By addition of an alkenylaluminum reagent to **44** and Swern oxidation of the resulting allylic alcohols **45**, enone **46** was formed. This compound is the substrate for the intramolecular Diels-Alder reaction.

Upon treatment of **46** with EtAlCl₂, the critical reaction proceeded to give the desired bicyclic compound **47**. The sulfide **47** then was treated with MCPBA, and Pummerer rearrangement then gave rise to the desired diketone **39**.

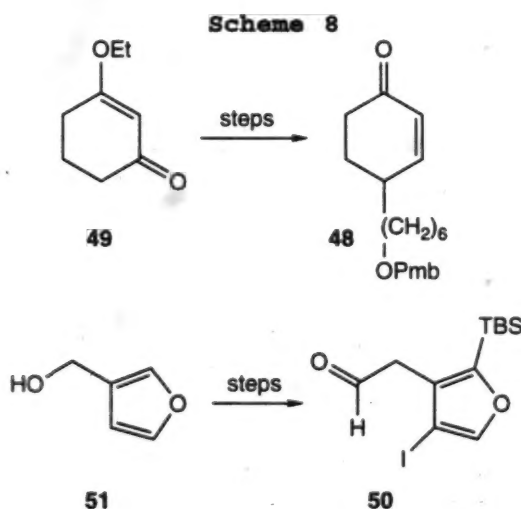
f. Danishefsky's Approach

All the above approaches directly address the introduction of the C(15)-C(16) bridgehead, which is present in both compounds **1** and **2**, and progress toward this end was accomplished through bond-reorganization strategies (cycloaddition or sigmatropic rearrangement).

However a route developed by Danishefsky's group reflects a different view of the problem.¹⁰ Its main focus is on gaining rapid access to a 15,16-dihydro ring system, with provision for the introduction of all the functional groups needed to obtain **1** and **2**.

The 15,16-dihydro ring system of **1** and **2** was reached through a proper sequencing of aldol and intramolecular Heck-type bond formation, using a 2,3,4-trisubstituted furan as a connecting device.

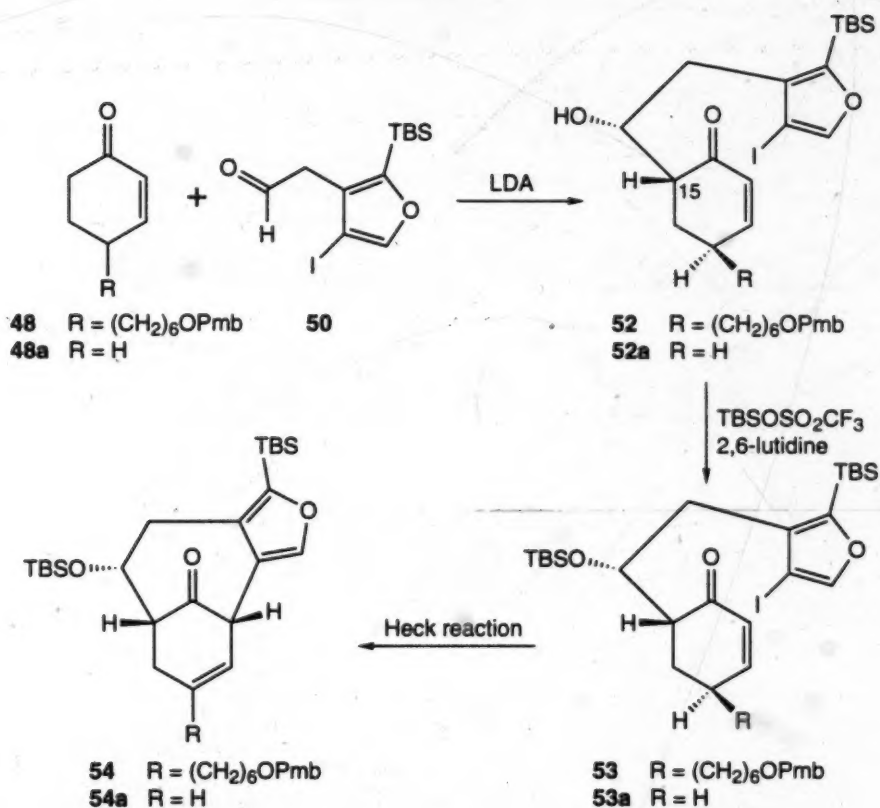
Enone **48**, a monocyclic precursor for the aldol reaction, was synthesized from compound **49** (Scheme 8). The synthesis of a 2,3,4-trisubstituted furan (**50**) commenced with commercially available **51**.



As shown in Scheme 9, aldol reaction of the α' -enolate derived from **48** with aldehyde **50** proceeded with high stereoselectivity, and afforded **52** in 91% yield. When cyclohexenone **48a** was condensed with aldehyde **50**, the stereoselective efficiency was diminished and the reaction provided **52a** in 79% yield. After protection of **52** and **52a**, the critical intramolecular Heck reaction of **53** and **53a** afforded **54** and **54a**, respectively.

With **54** and **54a** in hand, some functional group

Scheme 9

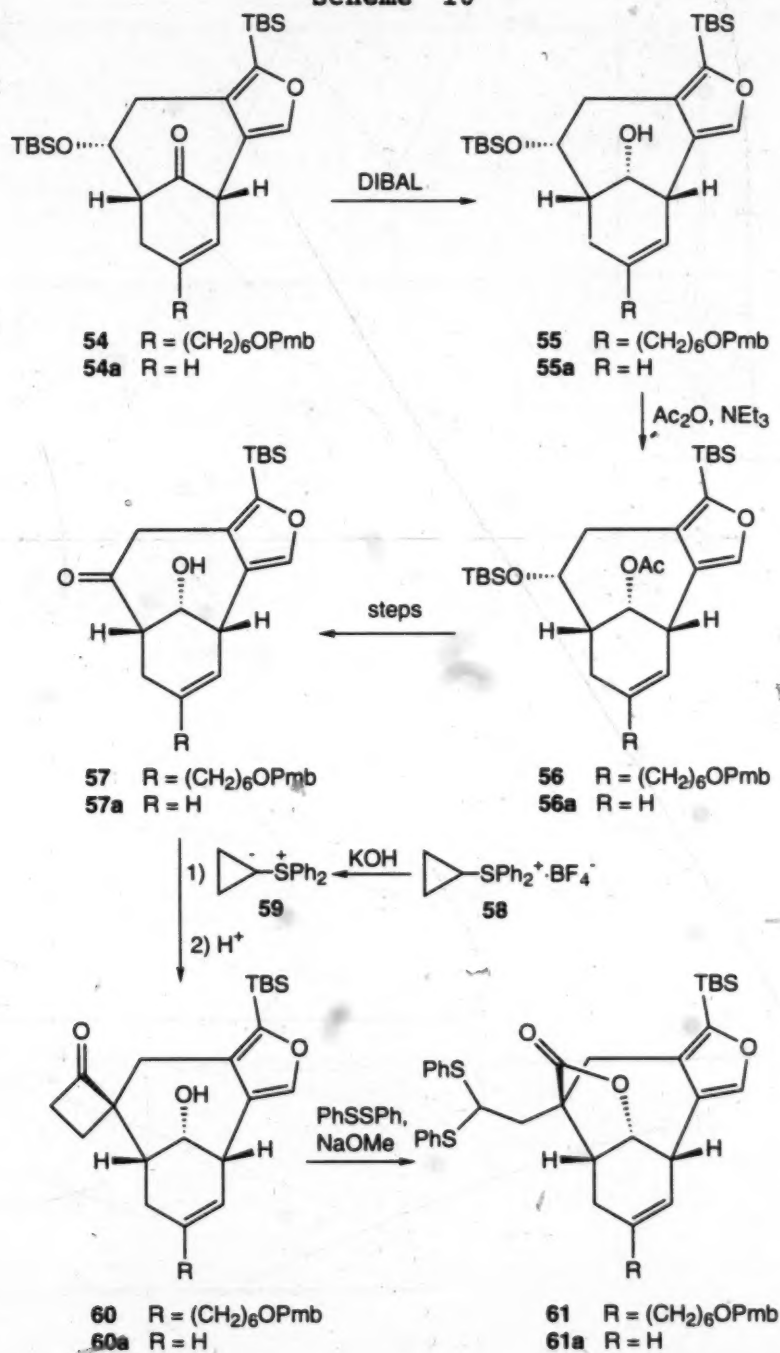


modifications, which could be helpful in reaching structures 1 or 2, were explored:

(1) Modification on the seven-membered ring^{10b}

(a) Reduction of 54 and 54a (Scheme 10) with diisobutylaluminum hydride provided a single alcohol in each case (55 and 55a), and acetylation gave the corresponding acetates (56 and 56a). Several straightforward steps then led to compounds 57 and 57a. Reaction of each of the latter with reagent 59, a relatively non-basic ylide, derived from the Trost sulfonium salt 58, occurred in a highly

Scheme 10

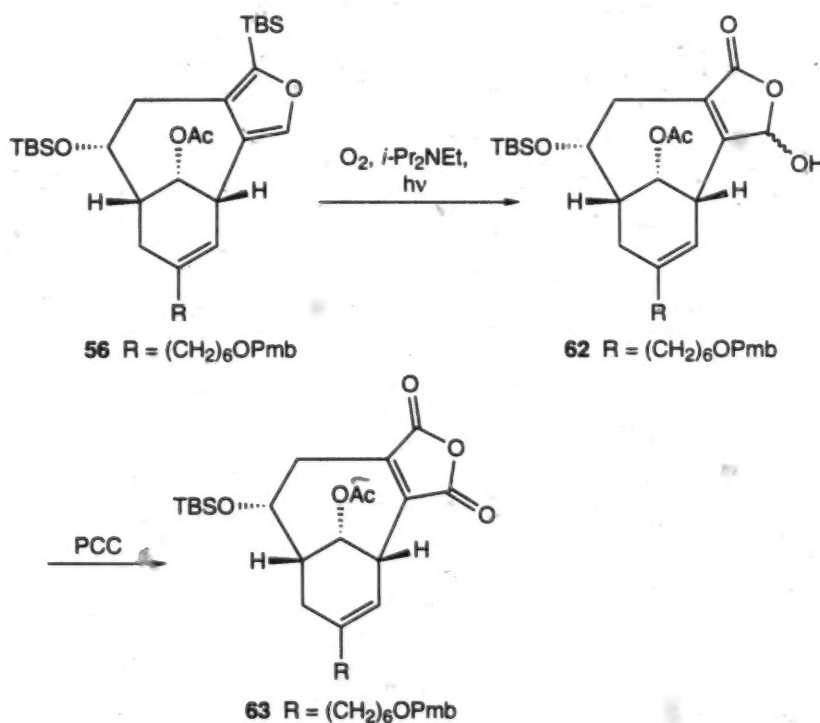


stereoselective fashion to give, after acidic treatment, the

spirocyclobutanones **60** and **60a**. Under standard conditions for bis-sulfenylative fragmentation of the cyclobutanone, compounds **61** and **61a** were obtained. Thus, a method for constructing the quaternary center in **1** and **2** was established.

(b) Photooxidation (Scheme 11) of the silylfuran **56** gave rise to compound **62** as a mixture of diastereomers. Further oxidation with PCC afforded the anhydride **63**, which showed an entry to the maleic anhydride moiety.

Scheme 11

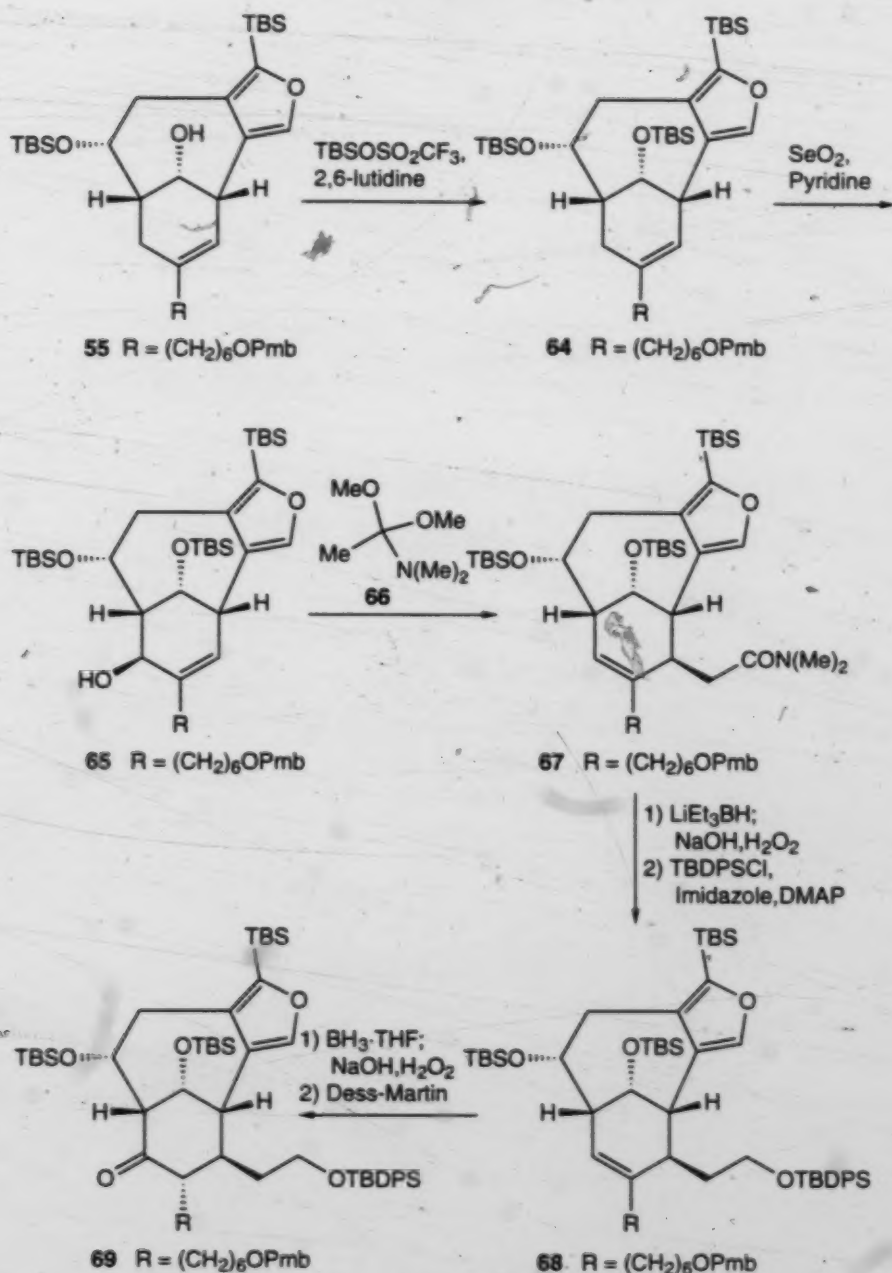


(2) Introduction of a chain in six-membered ring^{10a}

In a parallel series of reactions (Scheme 12),

silylation of **55** gave rise to **64**, and oxidation by selenium

Scheme 12



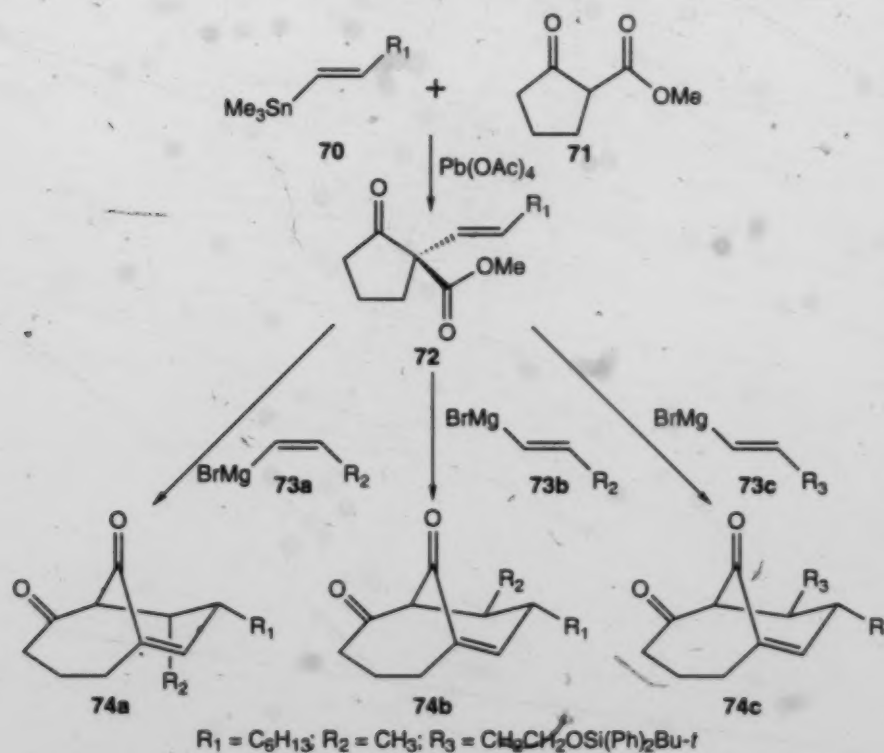
dioxide then afforded **65**. Reaction of **65** with **66** gave, upon

[3,3] sigmatropic rearrangement, the unsaturated amide **67**. The amide linkage was next reduced, and the resulting primary alcohol was protected by silylation. These operations led to **68**, from which point hydroboration and oxidation provided **69**.

g. Shair's Approach

Very recently, Shair et al.¹² described a bicyclic ring-forming reaction in a rapid and stereospecific synthesis of the core structure of **1**. The method is based on the idea¹ that transannular bond formation between C(10) and C(26) to generate the core skeleton may be feasible from a nine-

Scheme 13

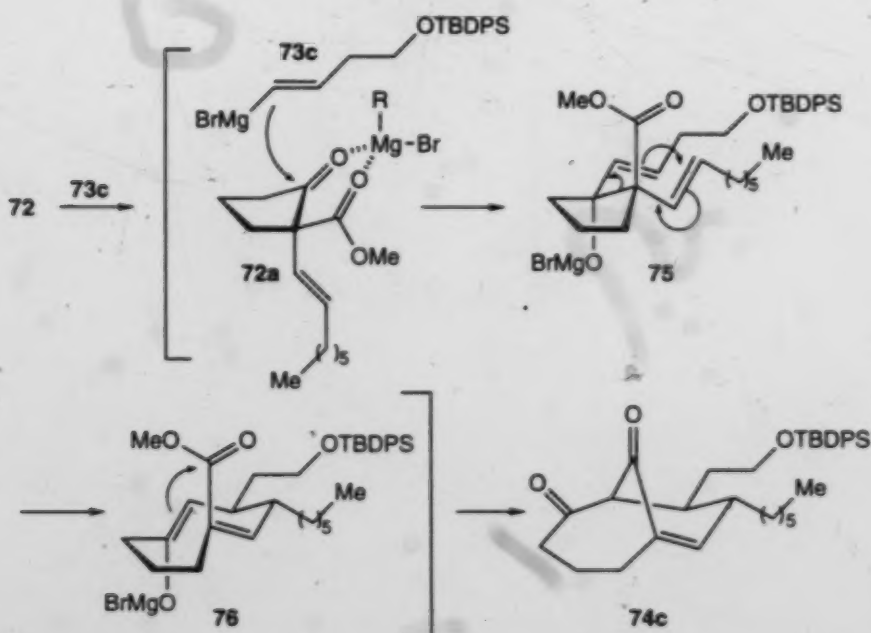


membered ring intermediate.

The synthesis (Scheme 13) was initiated by treatment of vinylstannane **70** with $\text{Pb}(\text{OAc})_4$, followed by exposure of the intermediate vinylated reagent to β -ketoester **71**, to deliver ketone **72**. Treatment of **72** with (*Z*)-1-propenylmagnesium bromide (**73a**) gave (65% yield) compound **74a**, which represents the desired bicyclo[4.3.1]deca-1(9)-ene ring system. The stereoselectivity of the bicyclization reaction was tested by exposure of ketone **72** to (*E*)-1-propenylmagnesium bromide **73b** and (*E*)-vinyl Grignard reagent **73c**. The major products (**74b** and **74c**) displayed a *trans* relationship between C(9) and C(17), corresponding to the stereochemistry of the side chains of **1** and **2**.

A mechanistic and stereochemical interpretation of this

Scheme 14



process is provided in Scheme 14. It is assumed that *anti*

addition of a vinyl Grignard reagent to chelated intermediate **72a** generates magnesium alkoxide **75**. An anionic oxy-Cope rearrangement of **75** through a chair transition state would afford the *E,E*-1,5-cyclononadiene intermediate **76**, as a bromomagnesium enolate.

The chair transition state shown in Scheme 14 would explain the stereochemical outcome observed with vinyl Grignard reagents **73a**, **73b** and **73c**. The presence of methyl ester may explain²⁸ the facile rearrangement of **75** under mild conditions (0 °C, magnesium alkoxide). Following the rearrangement, the bromomagnesium enolate **76** undergoes transannular acylation to provide **74c**, the core structure of **1** and **2**.

In this bicyclic ring-forming process, four stereochemical and structural issues [see C(9), C(10), and C(17), and the C(15)-C(16) trisubstituted bridgehead double bond] have been dealt with effectively in a single transformation, while assembling the core system of **1** and **2**. The reactions described above also demonstrate the feasibility of C(10)-C(26) transannular cyclization that has been proposed for the biosynthesis of **1** and **2**.¹

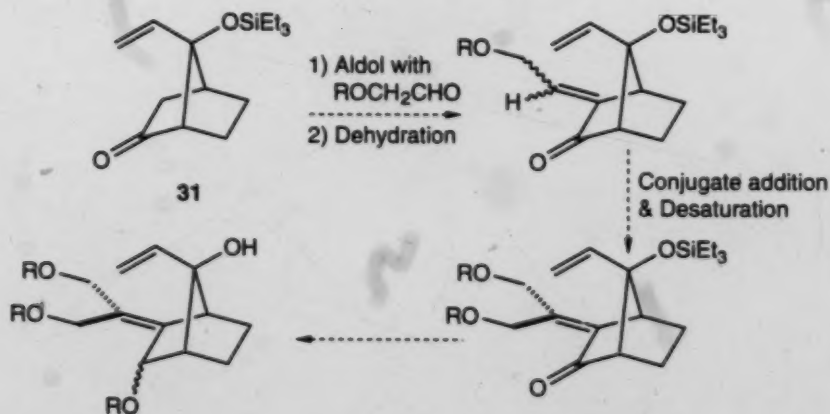
In summary, the intricate structure of **1** and **2** offers many opportunities for synthetic organic chemists to develop and apply new strategies, and it is not at all clear how the compounds will eventually be reached by total synthesis. All that is certain is that the substances represent very attractive targets.

Results and Discussion

Synthesis of bridgehead alkenic ketones **27** and **27a** by anionic oxy-Cope rearrangement²⁹ of 3-hydroxyl-1,5-dienes **26,26a** represents an initial test towards the total synthesis of both natural products CP-225,917 (**1**) and CP-263,114 (**2**). In order to examine the feasibility of employing the anionic oxy-Cope rearrangement for the construction of more advanced [4.3.1]-decadienones, especially for the introduction of substituents at C(14), which is a quaternary center in the natural products **1** and **2**, we decided to prepare **26,26a**-like substrates, having an oxygenated and doubly substituted group instead of a methyl group.

The synthetic plan for the preparation of the bicyclic dienol substrates is outlined in Scheme 15. Since we had been unable to effect aldol reactions on the siloxy ketone **31** with a ketone as the other carbonyl component,³⁰ we planned to do the aldol reaction with an aldehyde and to then carry

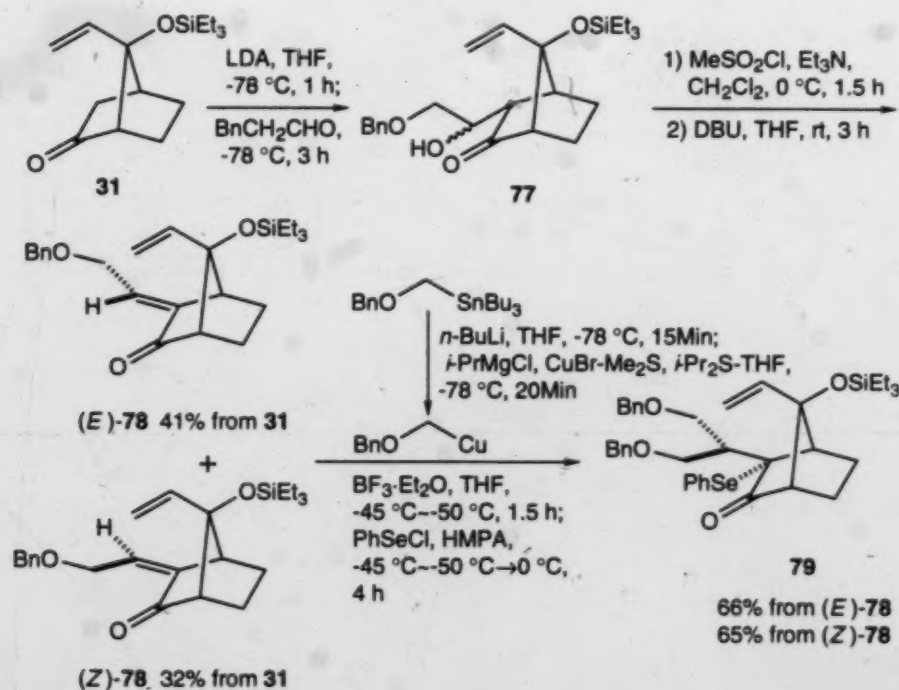
Scheme 15



out conjugate addition, followed by desaturation, to make the doubly substituted enone.

Work on this route began with aldol condensation of ketone **31**³⁰ with BnCH_2CHO ,³¹ as outlined in Scheme 16. The resulting crude aldols **77** (whose stereochemistry was not established) were converted into the corresponding

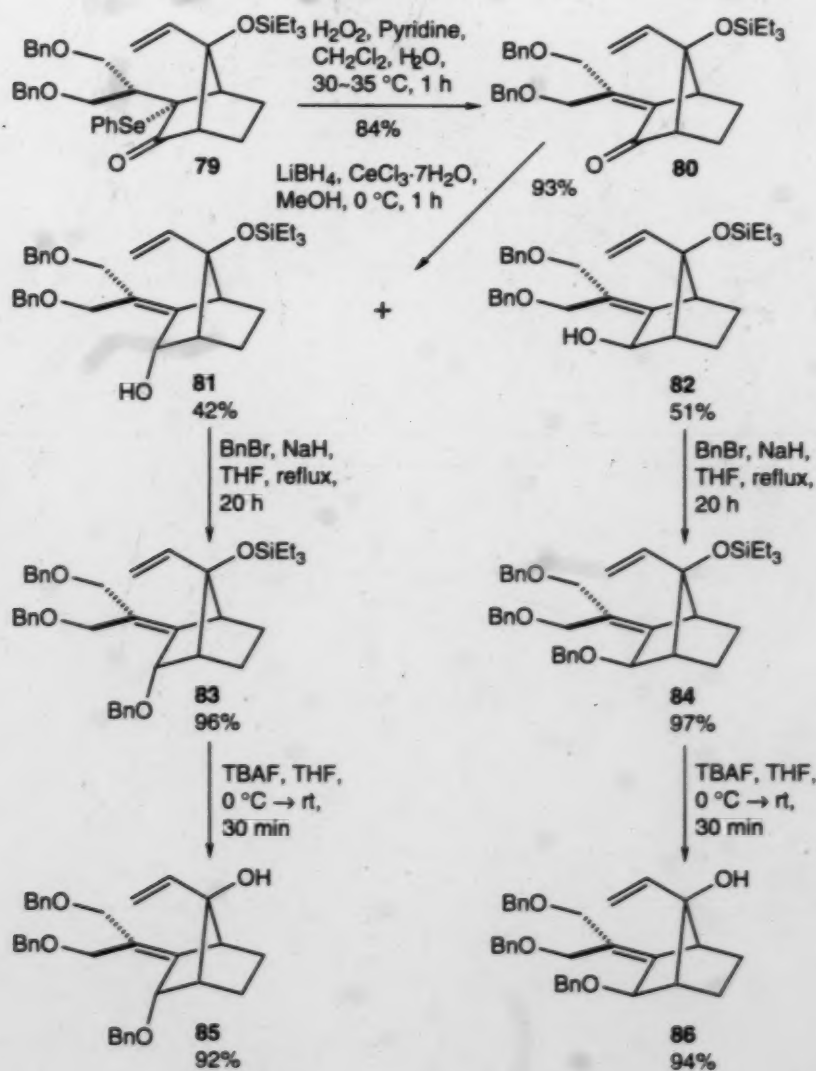
Scheme 16



mesylates and, without separation, the mesylates were treated with DBU , affording the desired enones **(E)-78** and **(Z)-78**, which were easily separated (*E*-isomer, 41% overall from **31**; *Z*-isomer, 32% overall from **31**). Both enones (*E*- and *Z*)-**78** underwent conjugate addition of freshly prepared [(benzyloxy)methyl]copper in the presence of boron trifluoride etherate.³² Subsequent enolate-trapping with

phenylselenenyl chloride³³ furnished the desired selenide **79** (66% from *E*-isomer, and 65% from *Z*-isomer). In this transformation, when we trapped the intermediate enolate with aqueous NH_4Cl , the product was simply the conjugate addition adduct (82% yield), which could not be converted into selenide **79** under standard selenization conditions (LDA,

Scheme 17

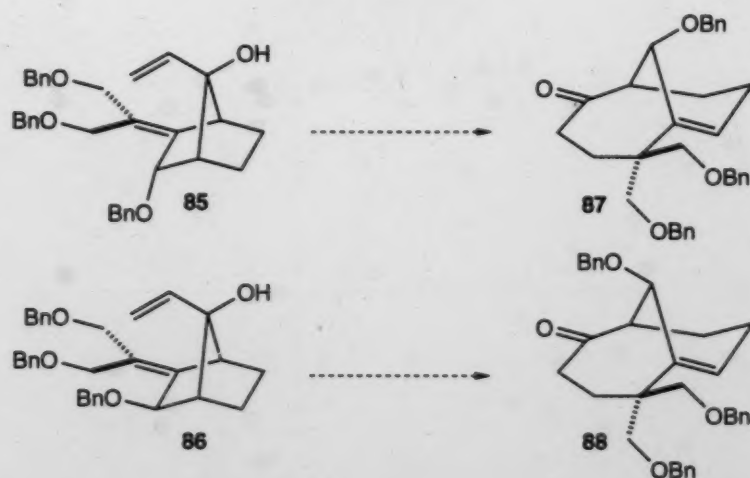


PhSeBr); only starting material was recovered from such experiments. When we trapped the intermediate enolate with PhSeCl, but without HMPA, about one third of the product was the simple conjugate adduct.

Oxidation of selenide **79** with H_2O_2 /pyridine (Scheme 17) led to selenoxide elimination, giving the doubly substituted α,β -unsaturated ketone **80** in 84% yield. Ketone **80** was then reduced, the best conditions being treatment with LiBH_4 in the presence $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$,³⁴ affording a mixture of alcohols, *endo*-**81** (42%) and *exo*-**82** (51%), which were separated and individually protected by benzylation (**81**→**83**, 96%, **82**→**84**, 97%). Desilylation of both **83** and **84** under standard conditions (TBAF, THF) gave the corresponding alcohols (**83**→**85**, 92%; **84**→**86**, 94%).

The stage was now set for the decisive anionic oxy-Cope rearrangement. We expected that, under suitable conditions, the hydroxydienes **85** and **86** would rearrange, affording,

Scheme 18



respectively, the desired bridgehead keto olefins **87** and **88** (Scheme 18).

We examined various anionic oxy-Cope conditions with *exo* isomer **86**, *endo* isomer **85**, or mixtures of both **85** and **86** (Table 2). However, none of these experiments was successful.

Table 2 Anionic oxy-Cope rearrangement of **85** and **86**

	Substrate	Conditions	Results
1	85 or mixture of 85 and 86	(Me ₃ Si) ₂ NK, PhMe, 100 °C, ⁸ 21 h	No desired product
2	mixture of 85 and 86	KH, 18-crown-6, THF, rt, ³⁵ 6 h	No desired product
3	86	KH, I ₂ , THF, HMPA, 0 °C → rt, ³⁶ 1 h	No desired product
4	86	K ₂ CO ₃ , decalin, reflux, 3 days ³⁷	No reaction
5	86	NaH, 18-crown-6, ³⁸ THF, reflux, 24 h	No reaction
6	86	(Me ₃ Si) ₂ NK, 18-crown-6, THF, ³⁹ rt, 3 h	No desired product

In view of the failure of the anionic oxy-Cope reaction, we tried ordinary thermal oxy-Cope conditions, but again, the results were disappointing (Table 3).

Moreover, no reaction was observed by heating compound **83** neat at 230 °C for 12 h.

It seemed that the doubly substituted substrates **85** and

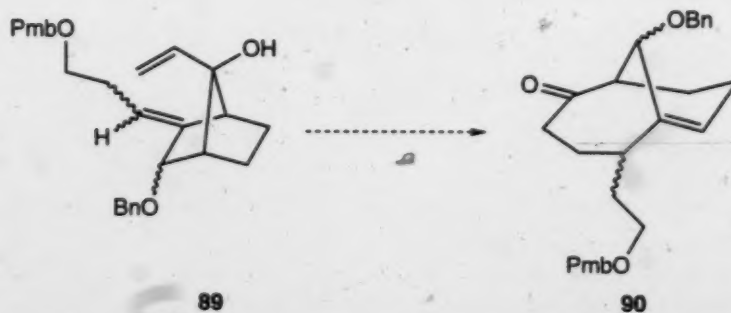
86 were not suited for the required transformation, and

Table 3 Attempted thermal oxy-Cope rearrangement of **86**

	Substrate	Conditions	Results
1	86	NMP, ⁴⁰ reflux, 7 h	No reaction
2	86	PdCl ₂ (PhCN) ₂ , ⁴¹ THF, rt, 12 h	No reaction
3	86	PdCl ₂ (PhCN) ₂ , NMP 140 °C, 24 h	No reaction
4	86	Hg(OCOCF ₃) ₂ , NaBH ₄ , CH ₂ Cl ₂ , ⁴² 30 min	No desired product

so we decided to try the oxy-Cope rearrangement with only one substituent on the double bond, such as in compounds **89**, and, for reasons described below, with a longer substituent (Scheme 19).

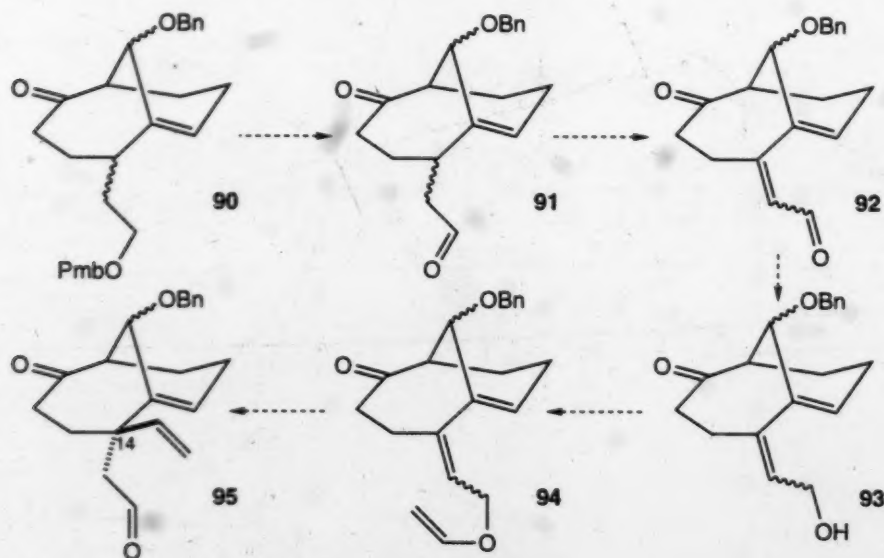
Scheme 19



We felt that the desired product of rearrangement (**90**) could be transformed eventually to a core structure of **1** and **2** with the quaternary center at C(14), as summarized in

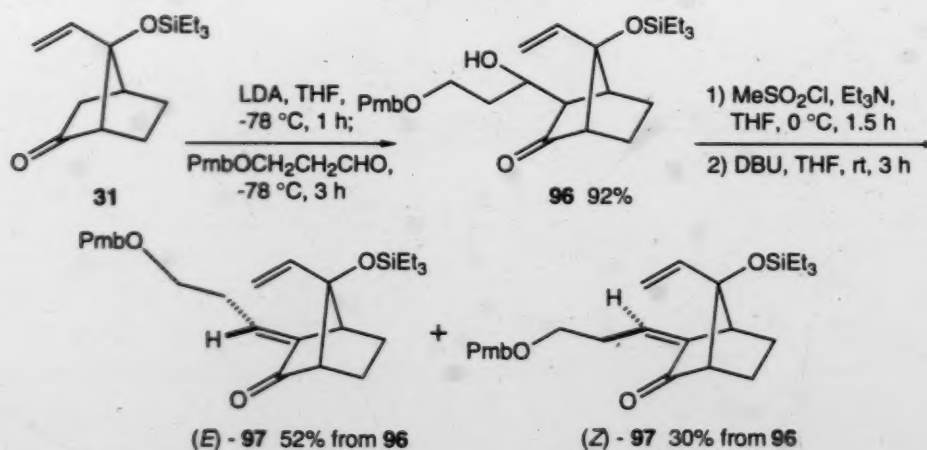
Scheme 20. The key step would be a Claisen rearrangement (94→95).⁴³ Only one of the two possible stereochemical outcomes of the Claisen rearrangement is shown in Scheme 20, since either stereochemistry at C(14) would be useful.

Scheme 20



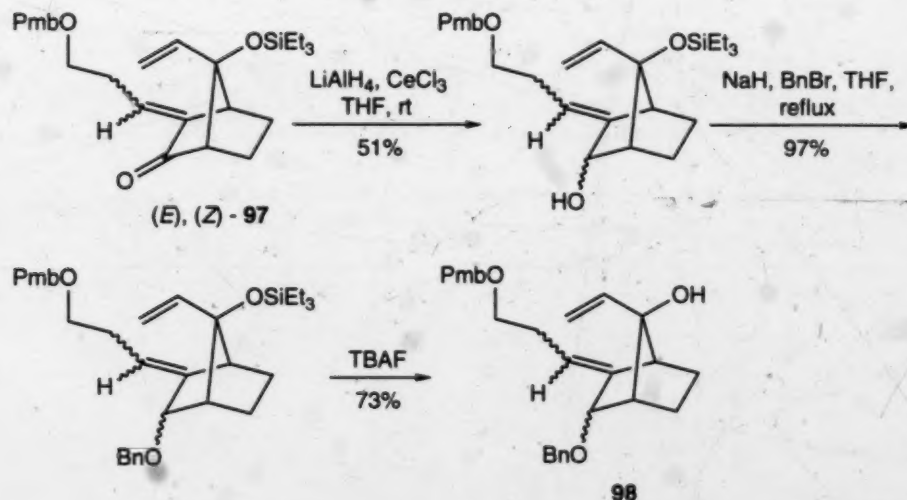
To this end, a short sequence of transformations was performed, as follows (Scheme 21). Aldol condensation of

Scheme 21



ketone **31**³⁰ with $\text{PmbOCH}_2\text{CH}_2\text{CHO}$ ⁴⁴ gave a single alcohol (**96**, 92%), whose stereochemistry was not established. After dehydration [**96** $\rightarrow$ (*E*)-**97** and (*Z*)-**97**], the desired enone (*E*)-**97** (52%) and (*Z*)-**97** (30%) were obtained.

Scheme 22

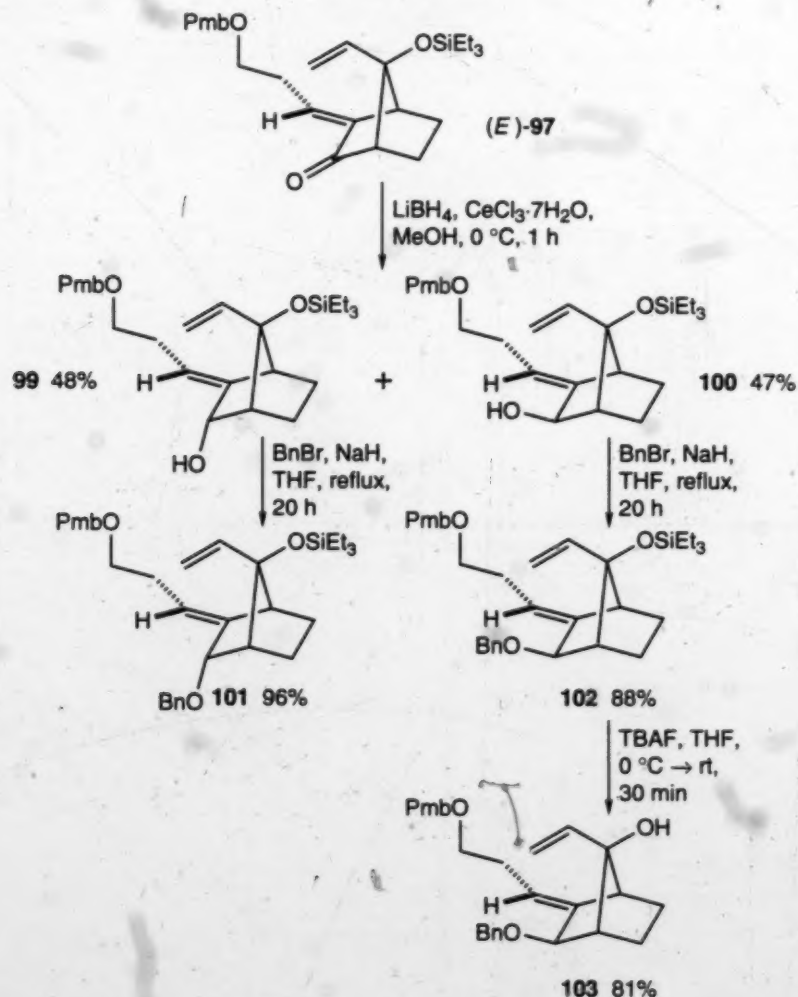


In the early exploratory experiments the compounds were not separated, and only a mixture of (*E*)-**97** and (*Z*)-**97** was taken further (Scheme 22). Reduction with LiAlH_4 and CeCl_3 in THF (51%), followed by benzylation (NaH , BnBr , 97%) and desilylation (TBAF, 73%), furnished the mixture of substrates **98**.

This sequence was then repeated, starting from the major isomer (*E*)-**97** (Scheme 23), and the *endo* and *exo* alcohols **99** and **100** were then separated. It was noticed that the use of LiBH_4 and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ ³⁴ gave a much better yield for the reduction of enone (*E*)-**97** than the usual NaBH_4 .

Several oxy-Cope rearrangement attempts on the mixture substrates **98** were made. The conditions and results are

Scheme 23



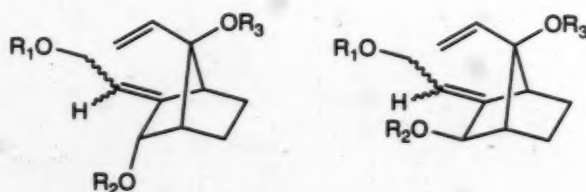
listed in Table 4.

At this point we realized that the number and the length of substituents on the double bond could be critical factors that determine the ease of rearrangement. The difference in this respect between compounds with a methyl⁸ and a (4-

Table 4 Attempted oxy-Cope rearrangement of **98**

	Conditions	Results
1	(Me ₃ Si) ₂ NK, PhMe ⁸ 100 °C, 18 h	No desired product
2	KH, Bu ₄ NI, THF reflux, 18 h	No reaction
3	KH, diglyme, 18-crown-6, ⁴⁵ rt, 40 h	No reaction
4	PdCl ₂ (MeCN) ₂ ⁴¹ THF, rt, 12 h	No reaction

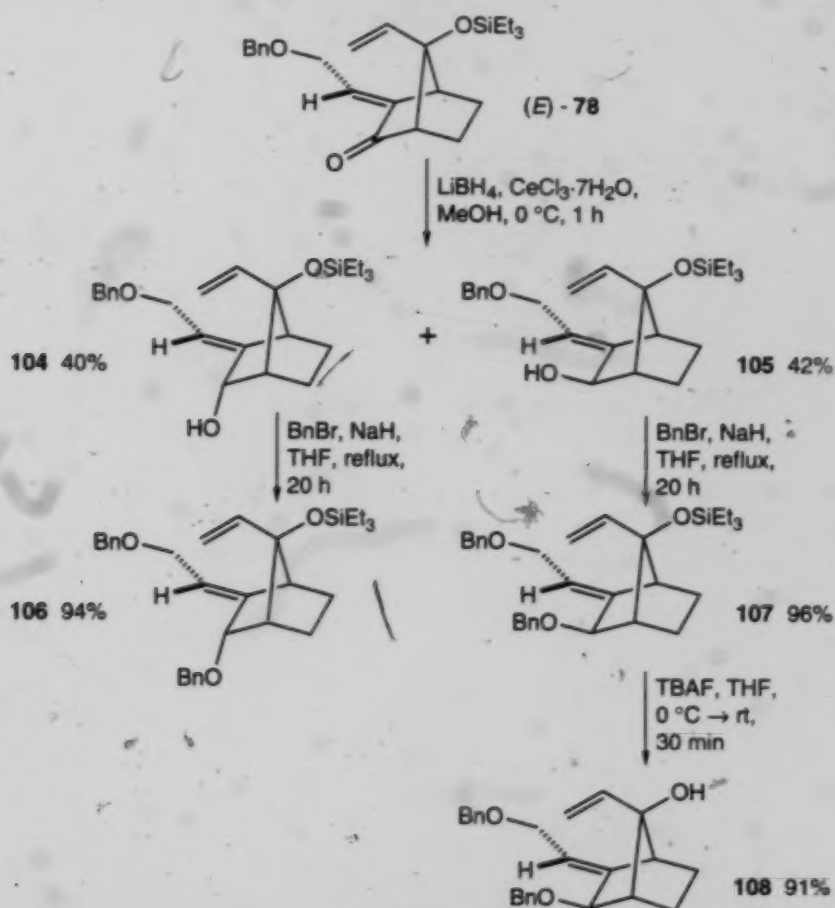
methoxyphenyl)methoxymethyl group on the double bond forced us to study the influence of substituent length and functionalization, and we examined the use of an oxygenated methyl group (see Figure 4).

**Figure 4** Model substrates

Specific examples of these model substrates could be prepared in the manner described earlier. As a matter of convenience, we started the synthesis (Scheme 24) with compound (*E*)-**78**, available from our earlier work. Reduction of enone (*E*)-**78**, followed by protection of the individual

isomeric products gave compounds **106** and **107**, as expected. Desilylation of **107** afforded the dienol **108**.

Scheme 24



With the required dienol **108** and silyl ether **106** in hand, we proceeded to try various oxy-Cope rearrangements (Table 5) and, eventually, we made some encouraging observations. The desired products **109** and **110** (Figure 5) were obtained for the first time, although the yields were not acceptable. Nevertheless, we decided to persist with this approach and to modify it.

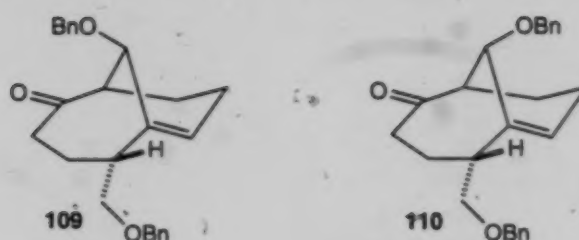


Figure 5 Structure of 109 and 110

Table 5 Attempted oxy-Cope rearrangement of 106 and 108

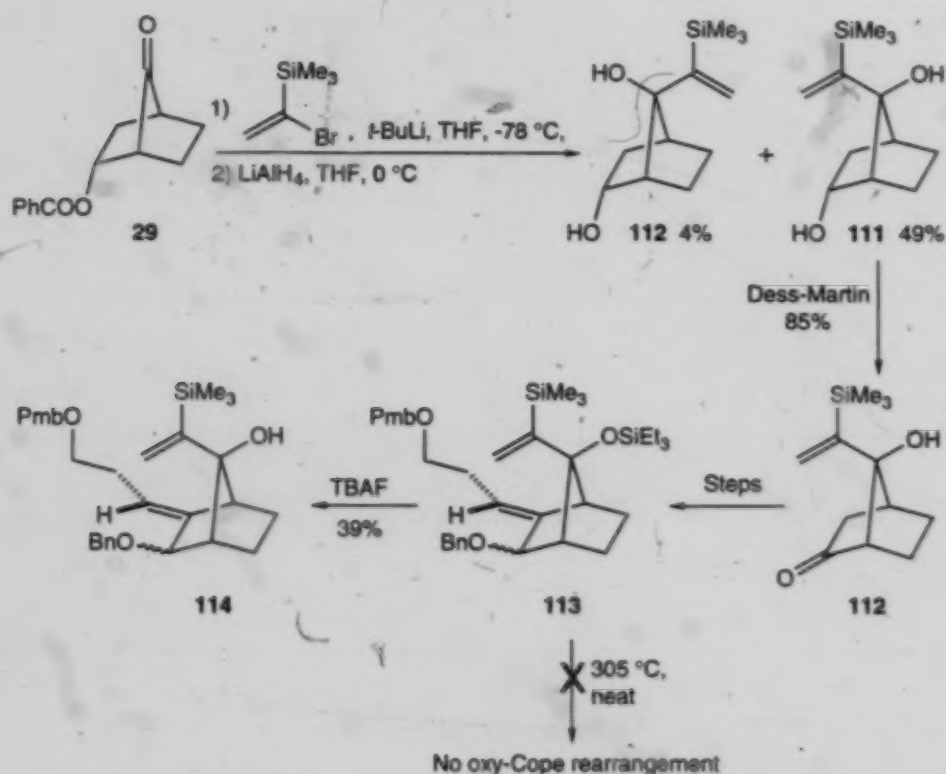
	Substrate	Conditions	Results
1	108	(Me ₃ Si) ₂ NK, PhMe, ⁸ 100 °C, 21 h	No desired product
2	108	Cs ₂ CO ₃ , decalin, reflux, 14 h	complex mixture Some SM recovered
3	108	(Me ₃ Si) ₂ NK, Decalin reflux, 4 h	complex mixture plus trace 109
4	106	(4-BrC ₆ H ₄) ₃ NSbCl ₆ ⁴⁶ rt, 15 min	complex mixture
5	106	<i>i</i> -Bu ₃ Al, CH ₂ Cl ₂ ⁴⁷ -78 °C → rt, 48 h	No desired product Some SM recovered
6	106	305 °C, neat, ⁴⁸ 3.5 h	Desired product 110 23%

On the basis of the experiments we had done so far, it was clear that the substrates we had tested were not ideal. We noticed from simple molecular models that the two double bond units might orient themselves far away from each other, and so we decided to introduce a substituted vinyl group at

C(7) of the [2.2.1]-bicyclic system. This modification should increase the proportion of conformations with the appropriate double bond carbons close together.

The initial substrate we planned to examine was the (trimethylsilyl)ethenyl alcohol **114**. The synthetic route is summarized in Scheme 25.

Scheme 25

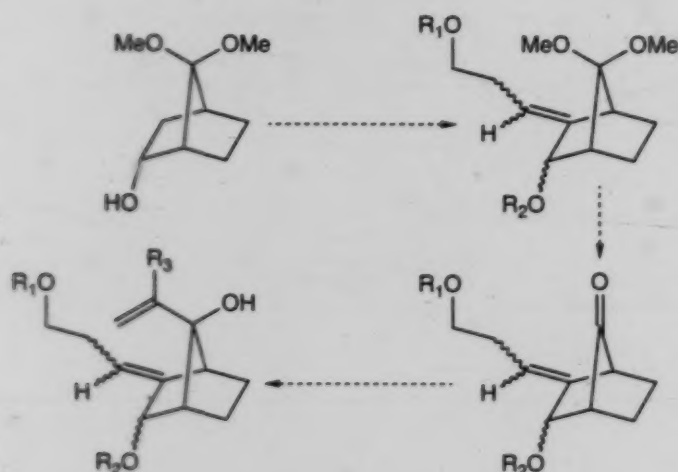


Ketone **29** was first converted into a mixture of tertiary alcohols with 1-(trimethylsilyl)vinyl lithium.^{49,50} Without separation, this mixture was reduced to a $> 12:1$ mixture of diols, with the desired isomer **111** being the major product. The geometry of **111** was confirmed by x-ray analysis.

After mild oxidation of **111** with the Dess-Martin reagent (85%), a sequence of reactions, starting from the resulting ketone **112**, was carried out under the conditions described earlier (cf. Scheme 21 and Scheme 23). However, due to the sensitivity of the vinylsilane unit this sequence proved troublesome. The yields were low and some reactions (e.g., the aldol condensation, dehydration, and reduction) could never be driven to completion. When silyl ether **113** was subjected to oxy-Cope conditions (305 °C, neat, 2.5 h), no desired product was detected.

This disappointing outcome forced us to try to develop a new route to reach **113** (so that we would have sufficient material for a thorough study). At the same time we also had to consider further modifications that might facilitate the oxy-Cope rearrangement.

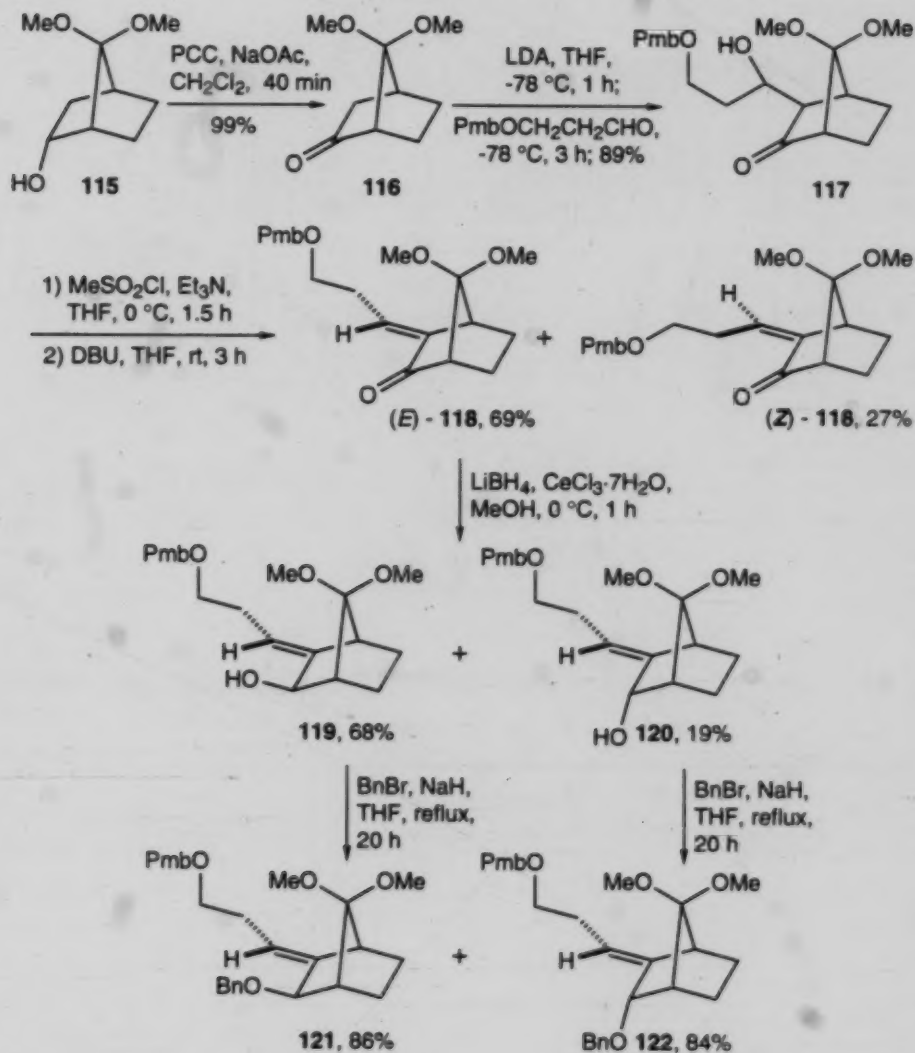
Scheme 26



We felt that our new proposed route should allow the preparation of different analogs of **114**, so that we could

assemble the modified substrates easily if one model substrate failed. We decided to explore the general strategy shown in Scheme 26. In this approach, a substituted vinyl group would be introduced at C(7) of the bicyclic system at a late stage.

Scheme 27

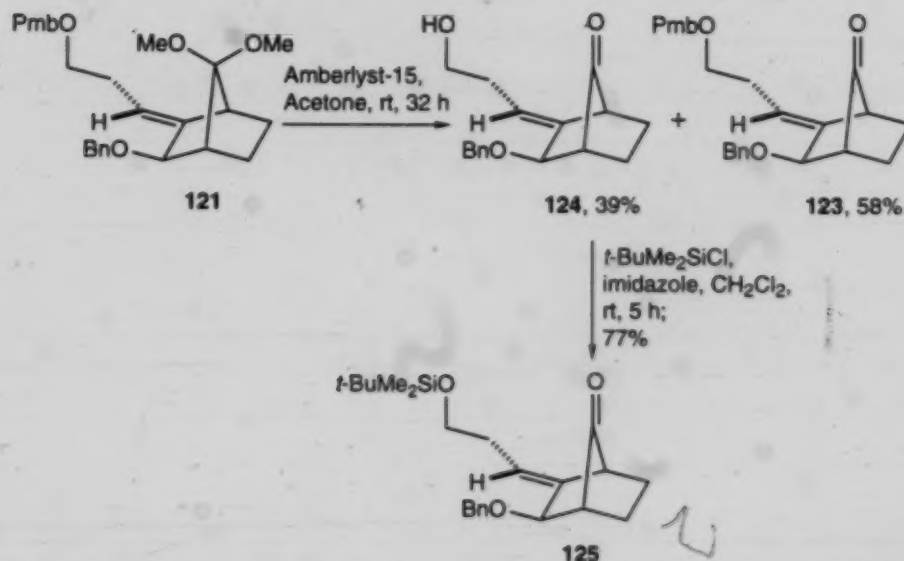


Starting with the oxidation of alcohol 115⁸ with PCC in

the presence of NaOAc, we then carried out an aldol condensation on ketone **116** (Scheme 27). Dehydration of aldol **117**, which was a single isomer, furnished enones (*E*)-**118** and (*Z*)-**118**. We used the major isomer [(*E*)-**118**] for further work. Treatment of enone (*E*)-**118** with LiBH_4 and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ gave two alcohol isomers **119** and **120**. Protection of the individual alcohols by benzylation afforded the ketals **121** and **122**.

Hydrolysis of dimethyl ketal **121** and **122** was expected to be straightforward, but many attempts had to be made in order to hydrolyze these ketals. We subsequently found that Amberlyst 15 in dry acetone⁵¹ worked well for **121**. It afforded ketone **123** (58%) and ketone alcohol **124** (39%).

Scheme 28



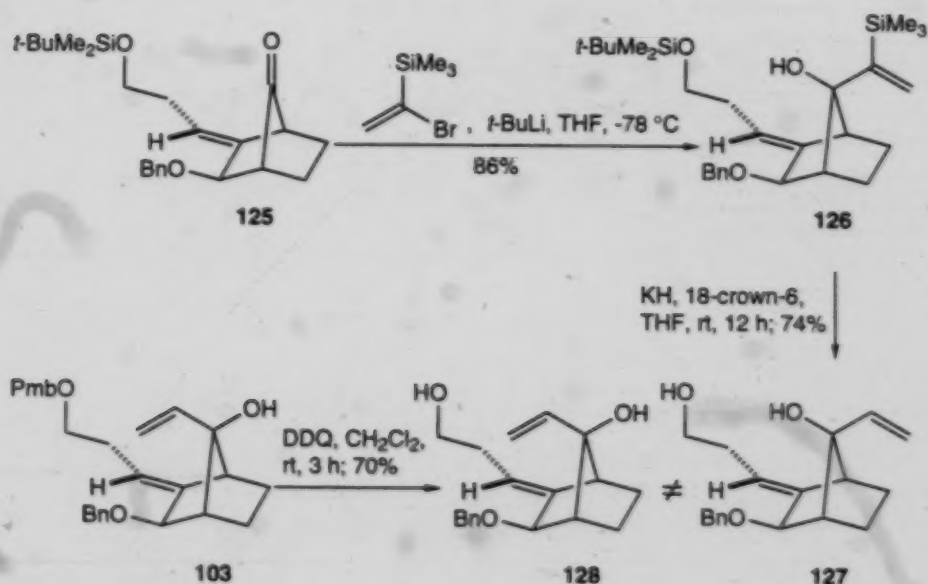
Ketone alcohol **124** was then converted into ketone silyl ether **125** (Scheme 28). However, when ketal **122** was subjected to

the same conditions (Amberlyst 15), the yield was sharply decreased.. We then found that the desired product from the hydrolysis of **122**, was unstable, and therefore, was unsuitable for further work.

We hoped that the same facial selectivity as was observed in earlier work with ketone **29** for reaction at the carbonyl⁸ would again be observed with our new ketones **123** and **125**.

We first attempted to react ketone silyl ether **125** with (1-bromoethenyl)trimethylsilane^{49,50} (Scheme 29). In the

Scheme 29

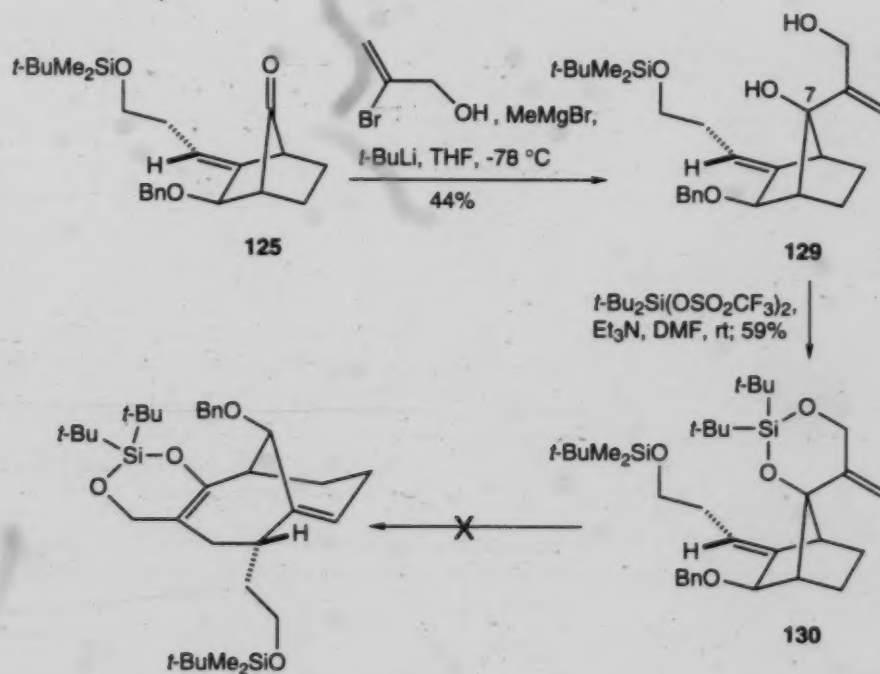


event, spectroscopic analysis of the material obtained from an attempted anionic oxy-Cope rearrangement allowed us to establish that the stereochemistry of the first step (**125** $\rightarrow$ **126**) was as shown, i.e. opposite to what we needed. From the attempted oxy-Cope rearrangement we had isolated some

desilylated material (**127**) and this proved to be different from **128**, which was made by deprotection of **103**, whose stereochemistry was firmly established. Consequently, we could assign the stereochemistry of **126**. We do not know how the silicon groups are lost, as the starting material **126** is stable to chromatography and aqueous workup. However, adventitious moisture during the attempted anionic oxy-Cope rearrangement would generate hydroxide ion, which might then act as a nucleophile towards silicon.

Before we had actually made the above stereochemical assignment to **126** we had also tried the addition of 2-bromopropen-1-ol ⁵² to ketone **125**⁵³ (Scheme 30). The resulting diol **129** could be converted into a spiro

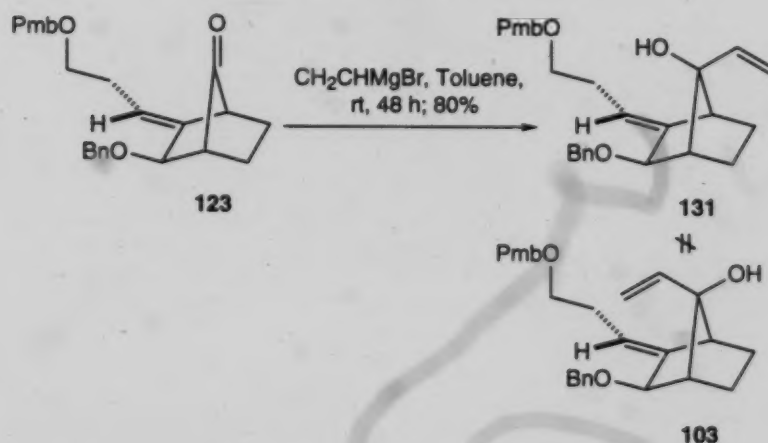
Scheme 30



compound⁵⁴ (**130**), which, of course, has a structural feature that restricts the conformations of the C(7) vinyl unit. However, when it was subjected to the thermal oxy-Cope conditions (NMP, reflux), none of the desired rearrangement product was detected. On this basis, the stereochemistry of **129** and **130** was tentatively assigned as shown. This assignment is consistent with the failure of spiro compound **130** to undergo oxy-Cope rearrangement, and is in line with our observations on **126** and **131** (see below). Unfortunately, we could not confirm the stereochemistry by NOE techniques.

A simpler model substance was also tested (Scheme 31). Vinylmagnesium bromide was added to ketone **123** to give **131**, which was not the same as compound **103**, obtained earlier by a stereochemically defined route. Thus, the stereochemistry of **131** could be assigned by spectroscopic comparison with **103**.

Scheme 31

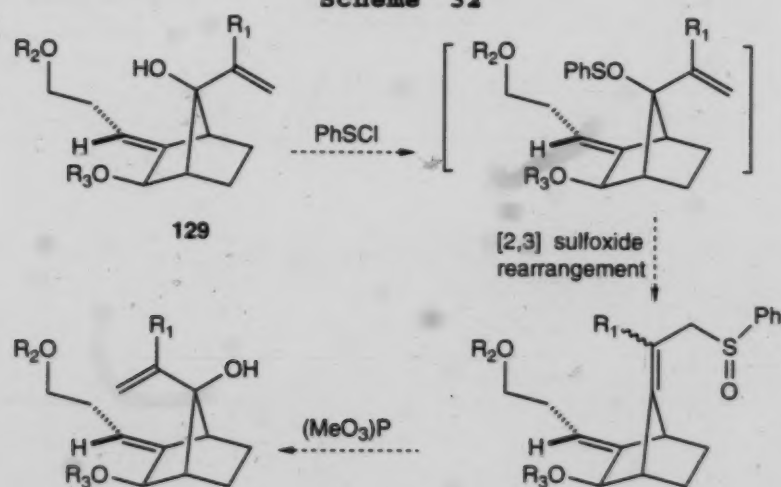


It was disappointing that the stereochemical outcome of these nucleophilic additions to the carbonyl occurred in an

undesired sense. Nevertheless methodology⁵⁵ is available that might allow inversion of the stereochemistry at C(7). This possibility is summarized in Scheme 32, but has not been tried.

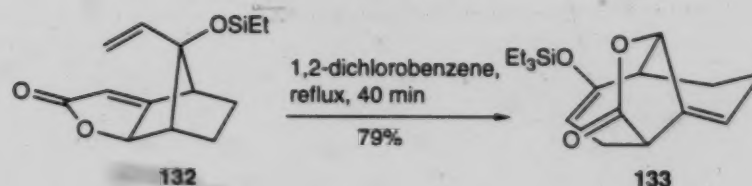
At this point, related work, by Dr. Sun of this laboratory, uncovered a smooth oxy-Cope rearrangement of silyl ether lactone **132**, giving the desired product **133** in

Scheme 32



79% yield. We reasoned this excellent outcome was the result of strain and twisting in the bicyclic system of **132** (Scheme 33).

Scheme 33

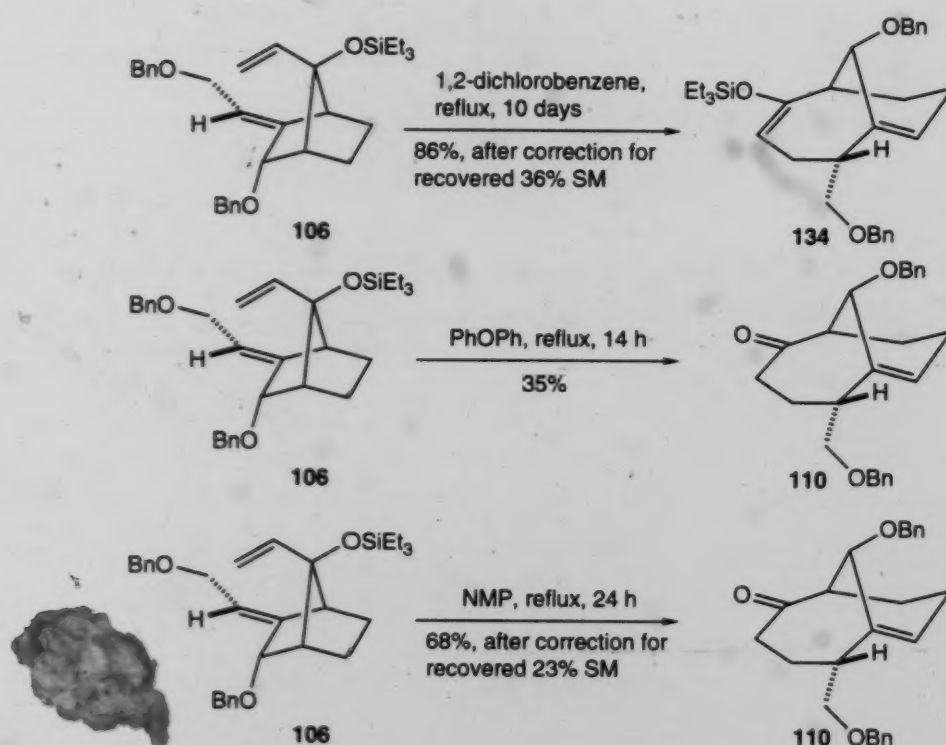


Examination of simple molecular models did not suggest that the strain in **132** is large, and so, in the light of Dr.

Sun's exciting result, we wondered if some of our own substrates might also be induced to rearrange well. Accordingly, a number of our substrates were heated in various solvents for long periods (Scheme 34 and Table 6), and we were indeed able to obtain the desired products.

Our experiments suggested that thermolysis of silyl

Scheme 34

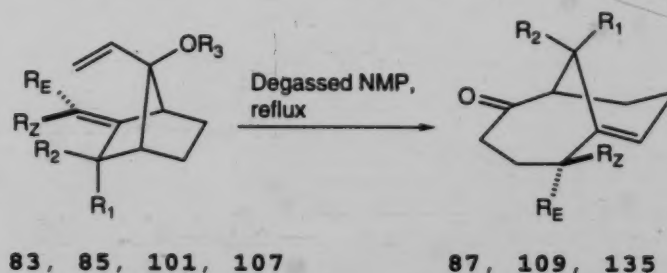


ethers (as opposed to alcohols, e.g. **85**, Table 6) in degassed NMP is a satisfactory procedure, and we have found that the reaction works smoothly. The value of NMP for silyl ethers has not been appreciated before, and the solvent has been recommended only for alcohols. By this route we were pleased to obtain product **87**, which was the first example made by

oxy-Cope rearrangement, with a quaternary center at C(14). An interesting observation was that with NMP these rearrangements directly gave desilylated ketone instead of the expected silyl enol ether. It is not clear at which stage the desilylation occurs.

It is not clear why NMP is so beneficial. The solvent has a large dipole moment (4 D^{56}), and our results may indicate that the transition state for a siloxy-Cope rearrangement is polar. The boiling point of NMP is sufficiently high for reaction to occur, but not so high as to cause thermal damage to the substrate. The loss of the silicon group probably results from transfer to NMP, which also provides a proton source needed to generate a ketone. There is precedent⁵⁷ for NMP behaving as a proton source.

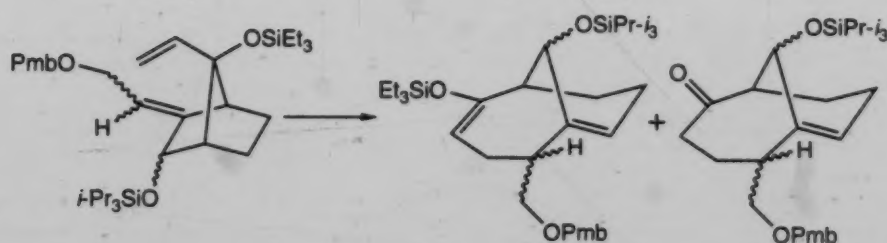
Table 6 Some results of siloxy-Cope rearrangement



Substance	Reaction time	Product and yield
83 $R_E = \text{CH}_2\text{OBn}, R_2 = \text{CH}_2\text{OBn},$ $R_1 = \text{OBn}, R_2 = \text{H},$ $R_3 = \text{SiEt}_3$	96 h	87 96% after correction for recovered 50% SM

$R_E = CH_2OBn, R_Z = CH_2OBn,$ 85 $R_1 = OBn, R_2 = H,$ $R_3 = H$	96 h	87 30% after correction for recovered 33% SM
$R_E = CH_2CH_2OPmb, R_Z = H,$ 101 $R_1 = OBn, R_2 = H,$ $R_3 = SiEt_3$	72 h	135 83%
$R_E = CH_2OBn, R_Z = H,$ 107 $R_1 = H, R_2 = OBn,$ $R_3 = SiEt_3$	72 h	109 86%

Scheme 35



In this laboratory, related work (Scheme 35), using a potentially better choice of protecting groups is now underway.

Conclusion

Oxy-Cope rearrangement, a key step of our approach to the challenging structures **1** and **2**, was studied in this thesis work. We have found that anionic rearrangement does not proceed if the ethylidene unit is modified by increase in chain length or in the number of substituents. However, in

refluxing NMP, siloxy-Cope rearrangement does take place and gives the desired products in good yield (after correction for recovered starting material). These results are now being used to reach more advanced compounds.

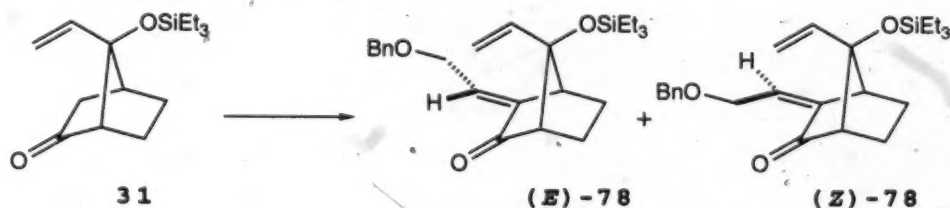
Experimental

General experimental procedures were the same as those used previously (see part 1). Stereochemical assignment of pairs of *E/Z* or *exo/endo* diastereomers was made by inspection of the ^1H NMR spectra according to chemical shift similarities with known corresponding compounds.^{8,30}

Preparation of LDA

n-BuLi (2.5 M in hexane, 1 equiv) was added dropwise to a stirred and cooled (0 °C) solution of *i*-Pr₂NH (1 equiv) in THF (ca. 18 mL per mmol *i*-Pr₂NH). Stirring was continued at 0 °C for 20 min before use.

(1 α ,3*E*,4 α ,7*R*^{*})-7-Ethenyl-3-[2-(phenylmethoxy)-ethylidene]-7-[(triethylsilyl)oxy]bicyclo[2.2.1]-heptan-2-one [(*E*)-78] and (1 α ,3*Z*,4 α ,7*R*^{*})-7-Ethenyl-3-[2-(phenylmethoxy)-ethylidene]-7-[(triethylsilyl)oxy]bicyclo[2.2.1]-heptan-2-one [(*Z*)-78].



A solution of ketone **31**^{8,30} (430 mg, 1.62 mmol) in THF (5.0 mL) was added dropwise to a stirred and cooled (-78 °C) solution of LDA (2.16 mmol) in THF (15 mL). Stirring was

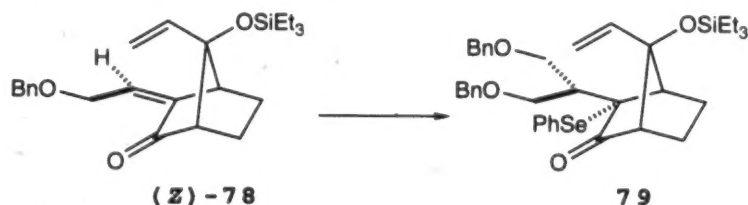
continued for 1 h, and then (phenylmethoxy)acetaldehyde³¹ (405 mg, 2.70 mmol) in THF (5 mL) was added in one portion. After 3 h (stirring), the mixture was quenched at -78 °C by addition of saturated aqueous NH₄Cl (2.0 mL). The cold bath was removed and the stirred mixture was allowed to warm to room temperature (over ca. 30 min), and diluted with Et₂O. The organic phase was washed successively with water and brine, dried (MgSO₄), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 10 cm), using 1:9 EtOAc-hexane, gave the crude aldols **77** (583 mg).

Et₃N (0.40 mL, 2.8 mmol) in CH₂Cl₂ (16 mL) was added to a stirred and cooled (0 °C) solution of the crude aldols (583 mg, ca. 1.40 mmol). MeSO₂Cl (0.22 mL, 2.8 mmol) was added dropwise and, after 1.5 h, the mixture was diluted with Et₂O, and filtered through a pad (1.5 x 2 cm) of flash chromatography silica gel. The pad was rinsed with Et₂O and the combined filtrates were evaporated. The residue was dissolved in THF (20 mL), and DBU (0.41 mL, 2.7 mmol) was added to the stirred solution. After 3 h, the mixture was diluted with Et₂O and washed successively with water, 10% aqueous hydrochloric acid, water and brine, dried (MgSO₄), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 18 cm), using 1:20 EtOAc-hexane, gave α,β -unsaturated ketones (**E**)-**78** (266 mg, 41%) and (**Z**)-**78** (208 mg, 32%), as pure (¹H NMR, 300 MHz), colorless oils. (**E**)-**78** had: FTIR (CH₂Cl₂ cast) 1738 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.58 (q, *J* = 7.7 Hz, 6 H), 0.94 (t, *J* = 7.7 Hz, 9 H), 1.41-1.60

(m, 2 H), 2.12-2.36 (m, 2 H), 2.67 (dd, $J = 4.5, 1.4$ Hz, 1 H), 3.03 (d, $J = 3.5$ Hz, 1 H), 4.15 (d, $J = 6.0$ Hz, 2 H), 4.51 (s, 2 H), 5.19 (dd, $J = 10.8, 0.6$ Hz, 1 H), 5.23 (dd, $J = 17.7$ Hz, 0.6 Hz, 1 H), 5.97 (dd, $J = 17.7, 10.8$ Hz, 1 H), 6.39 (td, $J = 6.0, 0.8$ Hz, 1 H), 7.14-7.41 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 6.37 (t'), 6.92 (q'), 22.97 (t'), 26.83 (t'), 48.65 (d'), 56.95 (d'), 66.98 (t'), 72.64 (t'), 84.54 (s'), 118.73 (t'), 126.73 (d'), 127.70 (d'), 127.83 (d'), 128.49 (d'), 137.84 (d'), 137.87 (s'), 143.52 (s'), 203.05 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{24}\text{H}_{35}\text{NaO}_3\text{Si}$ ($M + \text{H}$) 399.235549, found 399.234936.

(Z)-78 had: FTIR (CH_2Cl_2 cast) 1730 cm^{-1} ; ^1H NMR (CDCl_3 , 360 MHz) δ 0.59 (q, $J = 7.8$ Hz, 6 H), 0.94 (t, $J = 7.8$ Hz, 9 H), 1.48 (d, $J = 9.4$ Hz, 1 H), 1.52 (d, $J = 9.4$ Hz, 1 H), 2.10-2.37 (m, 2 H), 2.67 (dd, $J = 4.8, 1.6$ Hz, 1 H), 2.76 (dd, $J = 3.9, 1.3$ Hz, 1 H), 4.47 (d, $J = 11.7$ Hz, 1 H), 4.52 (d, $J = 11.7$ Hz, 1 H), 4.53 (dd, $J = 15.4, 5.7$ Hz, 1 H), 4.55 (d, $J = 15.4, 5.7$ Hz, 1 H), 5.19 (dd, $J = 10.8, 0.5$ Hz, 1 H), 5.24 (d, $J = 17.7$ Hz, 1 H), 5.89 (dd, $J = 5.7$ Hz, 1 H), 6.00 (dd, $J = 17.7, 10.8$ Hz, 1 H), 7.12-7.19 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 6.38 (t'), 6.93 (q'), 22.55 (t'), 27.33 (t'), 52.77 (d'), 58.48 (d'), 67.48 (t'), 72.80 (t'), 84.23 (s'), 118.69 (t'), 127.72 (d'), 127.86 (d'), 128.43 (d'), 133.67 (d'), 138.19 (s'), 138.25 (d'), 141.13 (s'), 204.16 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{24}\text{H}_{34}\text{NaO}_3\text{Si}$ ($M + \text{Na}$) 421.217493, found 421.218090.

(1 α ,3 β ,4 α ,7S*)-7-Ethenyl-3-[2-(phenylmethoxy)-1-
 [(phenylmethoxy)methyl]ethyl]-3-(phenylseleno)-7-
 [(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2-one (79).



Note that the stereochemistry at C(3) an arbitrary assignment.

i-PrMgCl (2.0 M in THF, 0.01 mL, 0.02 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of copper(I) bromide-dimethyl sulfide complex (83.4 mg, 0.406 mmol) in *i*-Pr₂S (1.5 mL) and THF (1.5 mL). Stirring at -78 °C was continued for 20 min before use.

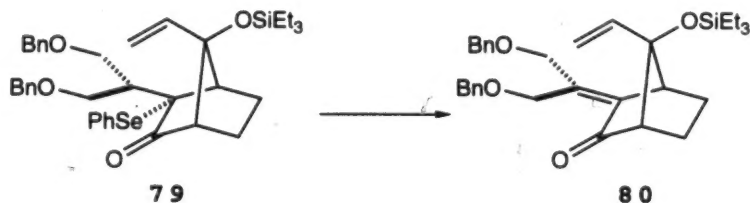
n-BuLi (2.5 M in hexane, 0.15 mL, 0.375 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of [(benzyloxy)methyl]trimethylstannane³² (152.7 mg, 0.372 mmol) in THF (2.0 mL), and stirring at -78 °C was continued for 15 min. The resulting yellow solution was transferred via a cooled cannula [the cannula was placed in a rubber tube, slit lengthwise and packed with solid CO₂] to the above copper(I) bromide solution, and the mixture was stirred at -78 °C for 20 min. A solution of (Z)-78 (67.3 mg, 0.169 mmol) in THF (2.0 mL) was added dropwise to the resulting brown homogeneous solution, and stirring at -78 °C was continued for 2 min. At that point, BF₃·Et₂O (0.05 mL, 0.4 mmol) was

injected in one portion. The cooling bath was changed to one maintained at -45 to -50 $^{\circ}\text{C}$, and stirring was continued for 1.5 h. A solution of PhSeCl (71.2 mg, 0.372 mmol) in THF (2.0 mL) was added dropwise, followed by HMPA (0.15 mL). The cooling bath was changed to one maintained at 0 $^{\circ}\text{C}$, and stirring was continued for 4 h. The reaction was quenched with saturated aqueous NH_4Cl (5.0 mL) at 0 $^{\circ}\text{C}$, and the mixture was extracted with Et_2O (3 x 5.0 mL). The combined organic extracts were washed with water (5.0 mL), brine (5.0 mL), dried and evaporated. Flash chromatography of the residue over silica gel (1 x 12 cm), using 1:20 EtOAc -hexane, gave **79** (74.2 mg, 65%) as a pure (^1H NMR, 360 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1732 cm^{-1} ; ^1H NMR (CDCl_3 , 360 MHz) δ 0.47-0.65 (m, 6 H), 0.83-1.02 (m, 9 H), 1.18 (ddd, $J = 13.4$, 8.8, 5.3 Hz, 1 H), 1.86-2.02 (m, 1 H), 2.28-2.42 (m, 1 H), 2.49 (ddd, $J = 12.2$, 8.8, 2.8 Hz, 1 H), 2.65 (dd, $J = 5.1$, 1.5 Hz, 1 H), 2.92 (ddd, $J = 12.6$, 7.0, 3.4 Hz, 1 H), 3.13 (dd, $J = 3.8$, 1.1 Hz, 1 H), 3.51 (dd, $J = 9.7$, 9.7 Hz, 1 H), 3.71 (dd, $J = 10.2$, 3.6 Hz, 1 H), 3.76 (dd, $J = 10.2$, 6.9 Hz, 1 H), 4.02 (dd, $J = 10.1$, 3.6 Hz, 1 H), 4.32 (d, $J = 11.9$ Hz, 1 H), 4.44 (d, $J = 11.9$ Hz, 1 H), 4.45 (d, $J = 11.7$ Hz, 1 H), 4.46 (d, $J = 11.7$ Hz, 1 H), 5.24 (d, $J = 10.7$ Hz, 1 H), 5.25 (d, $J = 17.9$ Hz, 1 H), 6.35 (dd, $J = 17.9$, 10.7 Hz, 1 H), 7.18-7.39 (m, 13 H), 7.59-7.66 (m, 2 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 6.39 (t'), 6.92 (q'), 22.12 (t'), 27.18 (t'), 47.02 (d'), 55.18 (d'), 56.33 (d'), 68.49 (t'), 69.80 (t'), 70.99 (s'), 72.69 (t'), 73.01 (t'), 85.04 (s'), 118.00 (t'), 127.37

(d'), 127.41 (d'), 127.54 (d'), 127.61 (d'), 128.23 (d'), 128.29 (d'), 128.51 (d'), 128.67 (d'), 129.22 (s'), 136.72 (d'), 138.51 (s'), 138.79 (s'), 140.02 (d'), 211.07 (s'); exact mass (HR electrospray) m/z calcd for $C_{38}H_{48}NaO_4Si^{80}Se$ (M + Na) 699.238479, found 699.238475.

The same procedure was used to convert (**E**)-**78** into **79** (66% yield).

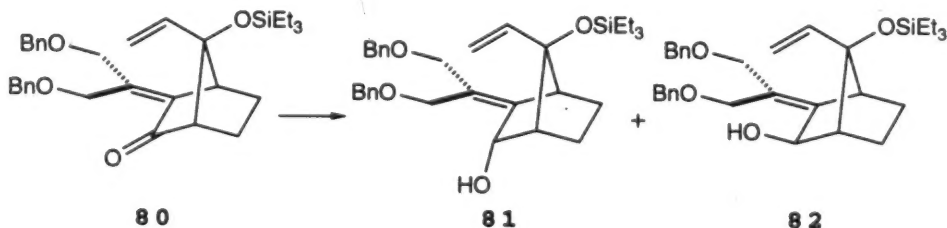
(1 α ,4 α ,7 R^*)-7-Ethenyl-3-[2-(phenylmethoxy)-1-[(phenylmethoxy)methyl]ethylidene]-7-[(triethylsilyl)-oxy]bicyclo[2.2.1]heptan-2-one (**80**).



H_2O_2 (30%, 0.17 mL, 1.7 mmol) was added dropwise to a stirred and warmed (30 °C) solution of **79** (226.7 mg, 0.336 mmol) and pyridine (0.12 mL, 1.5 mmol) in CH_2Cl_2 (40 mL), and stirring at 30-35 °C was continued for 1 h. The resulting mixture was washed with saturated aqueous $NaHCO_3$ (20 mL), 10% aqueous hydrochloric acid (20 mL), water (20 mL) and brine (20 mL), dried and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 1:10 EtOAc-hexane, gave **80** (146.2 mg, 84%) as a pure (^1H NMR, 360 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1725 cm^{-1} ; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.59 (q, $J = 7.9\text{ Hz}$, 6 H), 0.94 (t, $J = 7.9\text{ Hz}$, 9

H), 1.43-1.59 (m, 2 H), 2.10-2.37 (m, 2 H), 2.67 (dd, $J = 4.7, 1.7$ Hz, 1 H), 3.12 (dd, $J = 3.9, 1.6$ Hz, 1 H), 4.17 (d, $J = 11.5$ Hz, 1 H), 4.21 (d, $J = 11.5$ Hz, 1 H), 4.44 (d, $J = 11.8$ Hz, 1 H), 4.47 (d, $J = 11.8$ Hz, 1 H), 4.52 (d, $J = 12.0$ Hz, 1 H), 4.54 (d, $J = 12.0$ Hz, 1 H), 4.67 (d, $J = 12.7$ Hz, 1 H), 4.73 (d, $J = 12.7$ Hz, 1 H), 5.19 (dd, $J = 11.8, 0.6$ Hz, 1 H), 5.28 (dd, $J = 17.7, 0.6$ Hz, 1 H), 5.99 (dd, $J = 17.7, 11.8$ Hz, 1 H), 7.22-7.42 (m, 10 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 6.38 (t'), 6.94 (q'), 22.92 (t'), 26.93 (t'), 50.09 (d'), 58.57 (d'), 65.90 (t'), 67.59 (t'), 72.53 (t'), 73.00 (t'), 83.88 (s'), 118.79 (t'), 127.55 (d'), 127.71 (d'), 127.79 (d'), 128.32 (d'), 128.43 (d'), 138.19 (d'), 138.19 (s'), 138.61 (s'), 140.79 (s'), 141.80 (s'), 204.43 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{32}\text{H}_{42}\text{NaO}_4\text{Si}$ ($M + \text{Na}$) 541.275008, found 541.275138.

(1 α ,2 β ,4 α ,7 S^*)-7-Ethenyl-3-[2-(phenylmethoxy)-1-[(phenylmethoxy)methyl]ethylidene]-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2-ol (81) and (1 α ,2 α ,4 α ,7 S^*)-7-Ethenyl-3-[2-(phenylmethoxy)-1-[(phenylmethoxy)methyl]ethylidene]-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2-ol (82).



$\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (74.1 mg, 0.200 mmol) was added in one portion to a stirred solution of **80** (86.4 mg, 0.167 mmol) in dry MeOH (15 mL). After 10 min, the solution was cooled to 0 °C and LiBH_4 (2.0 M in THF, 0.10 mL, 0.20 mmol) was added dropwise. Stirring was continued at 0 °C for 1 h, the mixture was then diluted with Et_2O (10 mL), and filtered through a pad (1 x 2 cm) of flash chromatography silica gel. The pad was rinsed with Et_2O (30 mL) and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 2:8 EtOAc-hexane, gave **81** (36.8 mg, 42%) and **82** (44.2 mg, 51%) as pure (^1H NMR, 360 MHz), colorless oils: **81** had: FTIR (CH_2Cl_2 cast) 3432 cm^{-1} ; ^1H NMR (CDCl_3 , 360 MHz) δ 0.57 (q, J = 8.0 Hz, 6 H), 0.93 (t, J = 8.0 Hz, 9 H), 1.35 (ddd, J = 10.9, 9.2, 4.1 Hz, 1 H), 1.85 (dddd, J = 11.8, 11.8, 4.0, 4.0 Hz, 1 H), 2.00 (ddd, J = 11.8, 9.2, 4.3 Hz, 1 H), 2.11 (dddd, J = 11.4, 11.4, 4.5, 4.5 Hz, 1 H), 2.26 (dd, J = 4.3, 4.3 Hz, 1 H), 2.78 (d, J = 4.3 Hz, 1 H), 3.98 (d, J = 11.0 Hz, 1 H), 4.07 (d, J = 11.0 Hz, 1 H), 4.11 (d, J = 11.1 Hz, 1 H), 4.16 (d, J = 11.1 Hz, 1 H), 4.42-4.57 (m, 5 H), 5.15 (d, J = 10.7 Hz, 1 H), 5.27 (d, J = 17.7 Hz, 1 H), 5.95 (dd, J = 17.7, 10.7 Hz, 1 H), 7.24-7.39 (m, 10 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 6.53 (t'), 7.02 (q'), 18.87 (t'), 27.44 (t'), 49.64 (d'), 50.01 (d'), 68.34 (t'), 69.39 (t'), 70.68 (d'), 72.32 (t'), 73.02 (t'), 84.76 (s'), 117.71 (t'), 125.93 (s'), 127.65 (d'), 127.22 (d'), 127.95 (d'), 128.19 (d'), 128.43 (d'), 128.55 (d'), 137.56 (s'), 138.11 (d'), 138.46 (s'), 152.62 (s');

exact mass (HR electrospray) m/z calcd for $C_{32}H_{44}NaO_4Si$ ($M + Na$) 543.290658, found 543.291410.

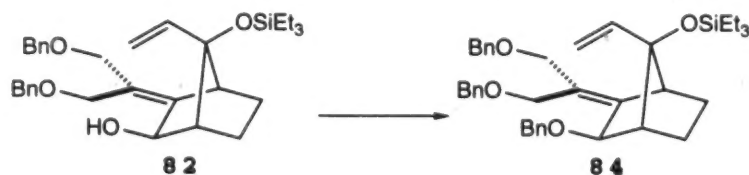
82 had: FTIR (CH_2Cl_2 cast) 3427 cm^{-1} ; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.59 (q, $J = 7.9\text{ Hz}$, 6 H), 0.93 (t, $J = 7.9\text{ Hz}$, 9 H), 1.07-1.23 (m, 2 H), 1.97-2.12 (m, 2 H), 2.14 (d, $J = 3.6\text{ Hz}$, 1 H), 2.51 (br s, 1 H), 2.96 (d, $J = 2.8\text{ Hz}$, 1 H), 4.08 (s, 1 H), 4.09 (d, $J = 10.6\text{ Hz}$, 1 H), 4.12 (d, $J = 10.6\text{ Hz}$, 1 H), 4.21 (d, $J = 11.4\text{ Hz}$, 1 H), 4.22 (d, $J = 11.4\text{ Hz}$, 1 H), 4.47 (d, $J = 11.7\text{ Hz}$, 1 H), 4.51 (d, $J = 11.7\text{ Hz}$, 1 H), 4.53 (d, $J = 12.6\text{ Hz}$, 1 H), 4.54 (d, $J = 12.6\text{ Hz}$, 1 H), 5.24 (dd, $J = 10.8, 1.3\text{ Hz}$, 1 H), 5.39 (dd, $J = 17.8, 1.3\text{ Hz}$, 1 H), 6.26 (dd, $J = 17.8, 10.8\text{ Hz}$, 1 H), 7.20-7.40 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 6.44 (t'), 6.97 (q'), 24.53 (t'), 26.81 (t'), 47.02 (d'), 52.98 (d'), 68.18 (t'), 68.40 (t'), 72.46 (t'), 72.79 (t'), 74.70 (d'), 86.30 (s'), 118.15 (t'), 127.62 (d'), 127.72 (d'), 127.85 (d'), 128.07 (s'), 128.37 (d'), 138.26 (s'), 138.43 (s'), 140.78 (d'), 152.47 (s'); exact mass (HR electrospray) m/z calcd for $C_{32}H_{44}NaO_4Si$ ($M + Na$) 543.290658, found 543.290727.

(1 α ,2 β ,4 α ,7 S^*)-[[7-Ethenyl-2-(phenylmethoxy)-3-[2-(phenylmethoxy)-1-[(phenylmethoxy)methyl]ethylidene]-bicyclo[2.2.1]hept-7-yl]oxy]triethylsilane (**83**).



NaH (80% dispersion in oil, 6.0 mg, 0.20 mmol) was added in one portion to a stirred and cooled (0 °C) solution of **81** (27.0 mg, 0.0519 mmol) in THF (2 mL). Stirring was continued for 15 min, and then BnBr (0.040 mL, 0.34 mmol) was added neat in one portion. The cold bath was removed and the mixture was stirred for 20 min, then refluxed for 20 h, cooled (0 °C), quenched (stirring) with MeOH (1 mL), diluted with brine (10 mL), and extracted with Et₂O (3 x 10 mL). The combined organic extracts were washed with brine (1 x 10 mL), dried and evaporated. Flash chromatography of the residue over silica gel (1 x 10 cm), using 1:10 EtOAc-hexane, gave **83** (30.6 mg, 96%) as a pure (¹H NMR, 300 MHz), colorless oil: FTIR (CH₂Cl₂ cast) unexceptional; ¹H NMR (CDCl₃, 300 MHz) δ 0.58 (q, J = 7.9 Hz, 6 H), 0.94 (t, J = 7.9 Hz 9 H), 1.43 (ddd, J = 11.5, 8.8, 4.3 Hz, 1 H), 1.75-1.94 (m, 2 H), 2.10 (dddd, J = 11.0, 11.0, 4.8, 4.8 Hz, 1 H), 2.34 (dd, J = 3.8, 3.8 Hz, 1 H), 2.85 (d, J = 4.2 Hz, 1 H), 4.03 (d, J = 10.5 Hz, 1 H), 4.11 (d, J = 11.8 Hz, 1 H), 4.13 (d, J = 10.5 Hz, 1

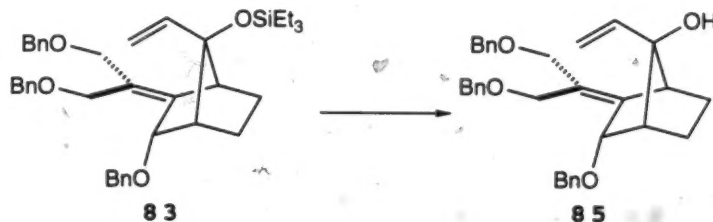
bicyclo[2.2.1]hept-7-yl]oxy]triethylsilane (84).



chromatography of the crude product over silica gel (1 x 10

pure (^1H NMR, 300 MHz), colorless oil; FTIR (CH_2Cl_2 cast) unexceptional; ^1H NMR (CDCl_3 , 300 MHz) δ 0.60 (q, $J = 7.9$ Hz, 6 H), 0.95 (t, $J = 7.9$ Hz, 9 H), 1.00-1.32 (m, 2 H), 1.95-2.16 (m, 2 H), 2.27 (d, $J = 3.6$ Hz, 1 H), 2.94 (d, $J = 2.7$ Hz, 1 H), 3.82 (s, 1 H), 4.08 (d, $J = 10.6$ Hz, 1 H), 4.09 (d, $J = 11.6$ Hz, 1 H), 4.17 (d, $J = 11.6$ Hz, 1 H), 4.18 (d, $J = 10.6$ Hz, 1 H), 4.24 (d, $J = 11.5$ Hz, 1 H), 4.36 (s, 2 H), 4.50 (d, $J = 11.5$ Hz, 1 H), 4.53 (s, 2 H), 5.13 (dd, $J = 10.8, 1.5$ Hz, 1 H), 5.28 (dd, $J = 17.6, 1.5$ Hz, 1 H), 6.22 (dd, $J = 17.6, 10.8$ Hz, 1 H), 7.20-7.40 (m, 15 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 6.61 (t'), 7.10 (q'), 24.54 (t'), 27.36 (t'), 47.85 (d'), 48.06 (d'), 67.81 (t'), 67.87 (t'), 71.20 (t'), 71.88 (t'), 72.52 (t'), 81.63 (d'), 86.69 (s'), 116.25 (t'), 127.42 (d'), 127.49 (d'), 127.67 (d'), 127.80 (d'), 127.97 (d'), 128.29 (d'), 128.32 (d'), 128.97 (s'), 138.41 (s'), 138.80 (s'), 138.97 (s'), 139.78 (d'), 148.54 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{39}\text{H}_{50}\text{NaO}_4\text{Si}$ (M + Na) 633.337609, found 633.336991.

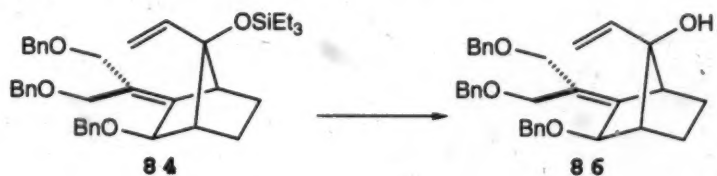
(1 α ,2 β ,4 α ,7 S^*)-7-Ethenyl-2-(phenylmethoxy)-3-[2-(phenylmethoxy)-1-[(phenylmethoxy)methyl]ethylidene]-bicyclo[2.2.1]heptan-7-ol (**85**).



TBAF (1.0 M in THF, 0.030 mL, 0.030 mmol) was added to a stirred and cooled (0 °C) solution of **83** (9.7 mg, 0.016 mmol) in THF (2 mL). The cold bath was removed, stirring was continued for 30 min, and the resulting mixture was diluted with Et₂O (5.0 mL) and washed with water and brine. The organic phase was dried and evaporated. Flash chromatography of the residue over silica gel (1 x 10 cm), using 1:10 EtOAc-hexane, gave **85** (7.3 mg, 92%) as a pure (¹H NMR, 300 MHz), colorless oil: FTIR (CH₂Cl₂ cast) 3424 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.51 (ddd, J = 12.0, 8.9, 3.9 Hz, 1 H), 1.84 (dddd, J = 12.0, 12.0, 4.1, 4.1, 1.4 Hz, 1 H), 1.97 (ddd, J = 11.7, 9.3, 4.4 Hz, 1 H), 2.13 (dddd, J = 11.7, 11.7, 4.1, 4.1 Hz, 1 H), 2.35 (dd, J = 4.0, 4.0 Hz, 1 H), 2.77 (d, J = 4.3 Hz, 1 H), 4.06 (d, J = 10.8 Hz, 1 H), 4.12 (d, J = 10.8 Hz, 1 H), 4.13 (d, J = 11.8 Hz, 1 H), 4.19 (d, J = 11.1 Hz, 1 H), 4.23 (d, J = 11.8 Hz, 1 H), 4.28 (d, J = 12.0 Hz, 1 H), 4.32 (d, J = 12.0 Hz, 1 H), 4.37 (d, J = 12.0 Hz, 1 H), 4.38 (d, J = 11.1 Hz, 1 H), 4.41 (d, J = 12.0 Hz, 1 H), 4.48 (br s,

1 H), 4.49 (s, 1 H), 5.21 (dd, $J = 10.8, 1.3$ Hz, 1 H), 5.45 (dd, $J = 17.4, 1.3$ Hz, 1 H), 6.08 (dd, $J = 17.4, 10.8$ Hz, 1 H), 7.20-7.38 (m, 15 H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 19.06 (t'), 27.15 (t'), 47.74 (d'), 49.57 (d'), 67.19 (t'), 67.90 (t'), 71.27 (t'), 71.86 (t'), 72.42 (t'), 77.83 (d'), 83.27 (s'), 116.71 (t'), 127.43 (d'), 127.46 (d'), 127.63 (d'), 127.73 (d'), 127.78 (d'), 128.19 (d'), 128.30 (d'), 128.32 (d'), 128.39 (d'), 129.21 (s'), 137.88 (s'), 138.73 (d'), 138.96 (s'), 146.40 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{33}\text{H}_{36}\text{NaO}_4$ ($M + \text{Na}$) 519.251130, found 519.251306.

(1 α ,2 α ,4 α ,7 S^*)-7-Ethenyl-2-(phenylmethoxy)-3-[2-(phenylmethoxy)-1-[(phenylmethoxy)methyl]ethylidene]-bicyclo[2.2.1]heptan-7-ol (86).

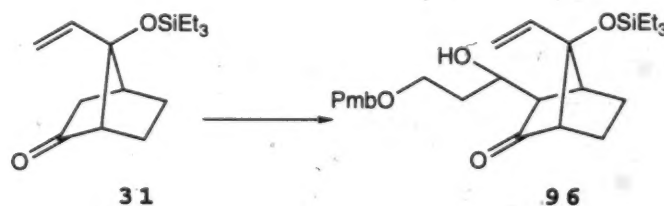


The procedure for making **85** was followed, using TBAF (1.0 M in THF, 0.085 mL, 0.085 mmol) and **84** (34.6 mg, 0.0567 mmol) in THF (2 mL). Flash chromatography of the crude product over silica gel (1 x 10 cm), using 1:10 EtOAc-hexane, gave **86** (26.4 mg, 94%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3427 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.08-1.35 (m, 2 H), 2.03-2.23 (m, 2 H), 2.28 (d, $J = 3.8$ Hz, 1 H), 2.73 (d, $J = 3.1$ Hz, 1 H), 3.90 (s, 1 H), 4.06 (d, $J =$

10.9 Hz, 1 H), 4.14 (d, $J = 11.6$ Hz, 1 H), 4.19 (d, $J = 10.9$ Hz, 1 H), 4.21 (d, $J = 11.6$ Hz, 1 H), 4.23 (d, $J = 11.4$ Hz, 1 H), 4.39 (d, $J = 12.0$ Hz, 1 H), 4.43 (d, $J = 12.0$ Hz, 1 H), 4.47 (d, $J = 12.1$ Hz, 1 H), 4.51 (d, $J = 11.4$ Hz, 1 H), 4.52 (d, $J = 12.1$ Hz, 1 H), 5.12 (dd, $J = 11.0, 1.2$ Hz, 1 H), 5.37 (dd, $J = 17.3, 1.2$ Hz, 1 H), 6.60 (dd, $J = 17.3, 11.0$ Hz, 1 H), 7.19–7.39 (m, 15 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 24.43 (t'), 27.34 (t'), 48.01 (d'), 49.69 (d'), 67.60 (t'), 71.32 (t'), 72.18 (t'), 82.25 (d'), 84.92 (s'), 112.77 (t'), 127.49 (d'), 127.61 (d'), 127.67 (d'), 127.82 (d'), 128.04 (d'), 128.34 (d'), 130.42 (s'), 138.19 (s'), 138.74 (s'), 138.83 (s'), 141.70 (d'), 147.70 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{33}\text{H}_{36}\text{NaO}_4$ ($M + \text{Na}$) 519.251130, found 519.251852.

(1 α ,3 α ,4 α ,7 R^*)-7-Ethenyl-3-[1-hydroxy-3-[(4-methoxyphenyl)methoxy]propyl]-7-[(triethylsilyl)oxy]-bicyclo[2.2.1]heptan-2-one (96).

Note that the stereochemistry at C(3) is an arbitrary assignment.

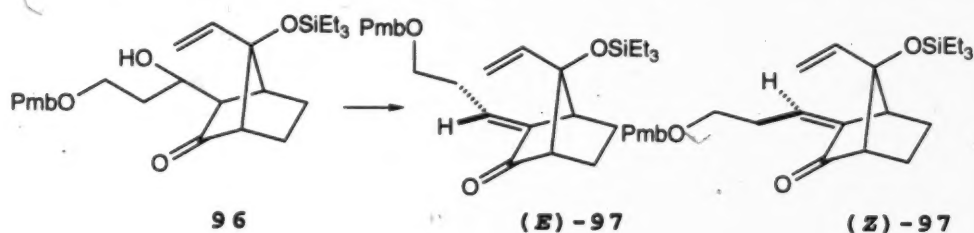


A solution of ketone **31**³⁰ (166.0 mg, 0.624 mmol) in THF (5.0 mL) was added dropwise to a stirred and cooled (-78°C)

solution of LDA (0.686 mmol, 1.1 equiv) in THF (10 mL). Stirring was continued for 1 h, and 3-[(4-methoxyphenyl)methoxy]propanal⁴⁴ (181.6 mg, 0.936 mmol) in THF (5 mL) was added dropwise. After 3 h, the mixture was quenched at -78 °C by addition of saturated aqueous NH₄Cl (4 mL). The cold bath was removed and the mixture was allowed to warm to room temperature over ca. 30 min, diluted with Et₂O, and washed successively with water and brine, dried and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:9 EtOAc-hexane, gave **96** (263 mg, 92%) as pure (¹H NMR, 300 MHz), colorless oil. The material, which was a single isomer of unestablished stereochemistry at the two newly-created asymmetric centers, had: FTIR (CH₂Cl₂ cast) 3506, 1729 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.56 (q, *J* = 7.9 Hz, 6 H), 0.92 (t, *J* = 7.9 Hz, 9 H), 1.39 (ddd, *J* = 11.1, 9.2, 3.2 Hz, 1 H), 1.50-1.67 (m, 2 H), 1.85 (dtd, *J* = 13.8, 6.9, 2.5 Hz, 1 H), 1.99 (d, *J* = 9.9 Hz, 1 H), 2.06-2.21 [m, including dd at δ 2.18 (*J* = 5.6, 2.0 Hz, 1 H), 2 H in all], 2.30 (dddd, *J* = 11.3, 11.3, 4.3, 4.3 Hz, 1 H), 2.67 (dd, *J* = 4.8, 1.2 Hz, 1 H), 3.50-3.66 (m, 2 H), 3.66-3.82 [m, including s at δ 3.80 (3 H), 4 H in all], 3.97 (ddd, *J* = 9.6, 5.8, 2.7 Hz, 1 H), 4.43 (s, 2 H), 5.29 (d, *J* = 10.8 Hz, 1 H), 5.33 (d, *J* = 17.7 Hz, 1 H), 6.06 (dd, *J* = 17.7, 10.8 Hz, 1 H), 6.90-6.83 (m, 2 H), 7.21-7.28 (m, 2 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 6.34 (t'), 6.91 (q'), 21.99 (t'), 28.82 (t'), 35.38 (t'), 47.12 (d'), 55.31 (d'), 56.29 (d'), 60.30 (q'), 66.31 (t'), 70.10 (d'), 72.81 (t'), 84.77 (s'), 113.77 (d').

119.78 (t'), 129.23 (d'), 130.70 (s'), 138.79 (d'), 159.19 (s'), 219.72 (s'); exact mass (HR electrospray) m/z calcd for $C_{26}H_{40}NaO_5Si$ ($M + Na$) 483.254273, found 483.254527.

(1 α ,3 E ,4 α ,7 R^*)-7-Ethenyl-3-[3-[(4-methoxyphenyl)-methoxy]propylidene]-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2-one (E)-97 and (1 α ,3 Z ,4 α ,7 R^*)-7-Ethenyl-3-[3-[(4-methoxyphenyl)methoxy]propylidene]-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2-one (Z)-97.



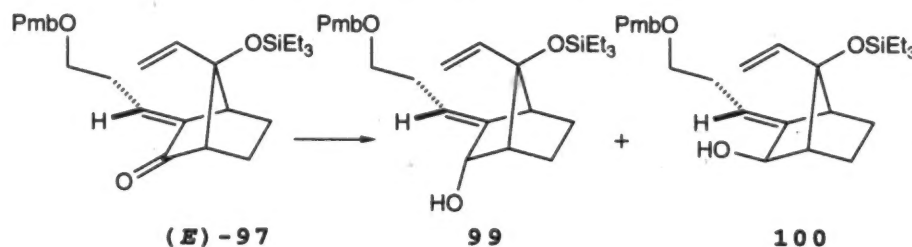
Et_3N (0.13 mL, 0.91 mmol) was added to a stirred and cooled (0 °C) solution of **96** (104.0 mg, 0.226 mmol) in THF (10 mL). $MeSO_2Cl$ (0.04 mL, 0.5 mmol) was added dropwise and, after 1.5 h, the mixture was diluted with Et_2O , and filtered through a pad (1.0 x 2 cm) of flash chromatography silica gel. The pad was rinsed with Et_2O and the combined filtrates were evaporated. The residue was dissolved in THF (20 mL), and DBU (0.41 mL, 2.7 mmol) was added to the stirred solution. After 3 h, the mixture was diluted with Et_2O and washed successively with water, 10% aqueous hydrochloric acid, water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 18 cm),

using 1:20 EtOAc-hexane, gave α,β -unsaturated ketones (**E**)-**97** (52.0 mg, 52%) and (**Z**)-**97** (30.0 mg, 30%), as pure (^1H NMR, 300 MHz), colorless oils. (**E**)-**97** had: FTIR (CH_2Cl_2 cast) 1733 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.58 (q, $J = 7.8\text{ Hz}$, 6 H), 0.94 (t, $J = 7.8\text{ Hz}$, 9 H), 1.37-1.56 (m, 2 H), 2.11-2.33 (m, 2 H), 2.40 (dt, $J = 7.5, 6.8\text{ Hz}$, 2 H), 2.65 (dd, $J = 4.5, 1.4\text{ Hz}$, 1 H), 2.96 (d, $J = 3.4\text{ Hz}$, 1 H), 3.50 (t, $J = 6.8\text{ Hz}$, 2 H), 3.80 (s, 3 H), 4.42 (s, 2 H), 5.13 (dd, $J = 10.8, 0.8\text{ Hz}$, 1 H), 5.21 (dd, $J = 17.7, 0.8\text{ Hz}$, 1 H), 5.93 (dd, $J = 17.7, 10.8\text{ Hz}$, 1 H), 6.30 (td, $J = 7.5, 0.8\text{ Hz}$, 1 H), 6.83-6.91 (m, 2 H), 7.17-7.28 (m, 2 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 6.39 (t'), 6.95 (q'), 23.03 (t'), 26.92 (t'), 29.80 (t'), 48.24 (d'), 55.32 (q'), 57.49 (d'), 68.45 (t'), 72.77 (t'), 84.61 (s'), 113.83 (d'), 118.52 (t'), 128.00 (d'), 129.29 (d'), 130.31 (s'), 137.93 (d'), 143.85 (s'), 159.27 (s'), 203.19 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{26}\text{H}_{38}\text{NaO}_4\text{Si}$ ($M + \text{Na}$) 465.243708, found 465.243313.

(**Z**)-**97** had: FTIR (CH_2Cl_2 cast) 1727 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.59 (q, $J = 7.8\text{ Hz}$, 6 H), 0.93 (t, $J = 7.8\text{ Hz}$, 9 H), 1.42-1.56 (m, 2 H), 2.06-2.35 (m, 2 H), 2.63 (dd, $J = 4.8, 1.7\text{ Hz}$, 1 H), 2.69 (dd, $J = 3.9, 1.7\text{ Hz}$, 1 H), 2.73-2.98 (m, 2 H), 3.47 (td, $J = 6.4, 1.1\text{ Hz}$, 2 H), 3.80 (s, 3 H), 4.40 (s, 2 H), 5.14 (dd, $J = 10.8, 0.8\text{ Hz}$, 1 H), 5.22 (dd, $J = 17.7, 0.8\text{ Hz}$, 1 H), 5.84 (t, $J = 7.4\text{ Hz}$, 1 H), 5.98 (dd, $J = 17.7, 10.8\text{ Hz}$, 1 H), 6.83-6.90 (m, 2 H), 7.20-7.27 (m, 2 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 6.38 (t'), 6.93 (q'), 22.53 (t'), 27.51 (t'), 28.89 (t'), 53.12 (d'), 55.30 (q'),

59.04 (d'), 69.00 (t'), 72.25 (t'), 84.15 (s'), 113.77 (d'), 118.43 (t'), 129.24 (d'), 130.60 (s'), 133.88 (d'), 138.30 (d'), 141.94 (s'), 159.18 (s'), 204.57 (s'); exact mass (HR electrospray) m/z calcd for $C_{26}H_{38}NaO_4Si$ ($M + Na$) 465.243708, found 465.244015.

(1 α ,2 β ,3 E ,4 α ,7 S^*)-7-Ethenyl-3-[3-[(4-methoxyphenyl)methoxy]propylidene]-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2-ol (**99**) and (1 α ,2 α ,3 E ,4 α ,7 S^*)-7-Ethenyl-3-[3-[(4-methoxyphenyl)methoxy]propylidene]-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2-ol (**100**).



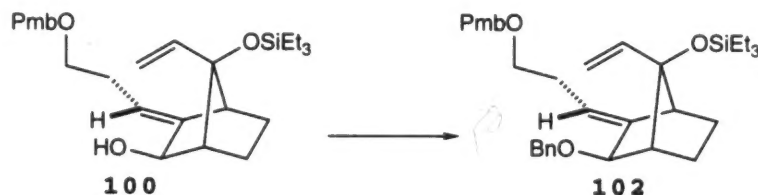
The procedure for making **81** and **82** was followed, using $CeCl_3 \cdot 7H_2O$ (23.0 mg, 0.0617 mmol), $LiBH_4$ (2.0 M in THF, 0.033 mL, 0.066 mmol), **(E)-97** (24.8 mg, 0.0561 mmol), and dry MeOH (5 mL). Flash chromatography of the crude product over silica gel (1 x 10 cm), using 2:8 EtOAc-hexane, gave **99** (12.0 mg, 48%) and **100** (11.7 mg, 47%) as pure (^1H NMR, 360 MHz), colorless oils. **99** had: FTIR (CH_2Cl_2 cast) 3416 cm^{-1} ; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.57 (q, $J = 7.9$ Hz, 6 H), 0.93 (t, $J = 7.9$ Hz, 9 H), 1.20-1.31 (m, 1 H), 1.57 (br s, 1 H), 1.72-1.93 (m, 2 H), 2.04-2.18 (m, 2 H), 2.34 (dtd, $J = 6.3, 6.3, 1.4$ Hz, 2

H) 2.74 (d, $J = 4.2$ Hz, 1 H), 3.46 (t, $J = 6.9$ Hz, 2 H), 3.80 (s, 3 H), 4.31 (br s, 1 H), 4.44 (s, 2 H), 5.11 (dd, $J = 10.8, 1.4$ Hz, 1 H), 5.21 (dd, $J = 17.6, 1.4$ Hz, 1 H), 5.35 (td, $J = 6.9, 1.0$ Hz, 1 H), 5.95 (dd, $J = 17.6, 10.8$ Hz, 1 H), 6.83-6.92 (m, 2 H), 7.21-7.30 (m, 2 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 6.54 (t'), 7.02 (q'), 18.66 (t'), 28.45 (t'), 29.80 (t'), 47.64 (d'), 50.83 (d'), 55.33 (q'), 69.57 (t'), 72.44 (d'), 72.60 (t'), 84.87 (s'), 113.81 (d'), 117.30 (t'), 117.99 (d'), 129.30 (d'), 130.59 (s'), 138.02 (d'), 149.95 (s'), 159.23 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{26}\text{H}_{40}\text{NaO}_4\text{Si}$ (M + Na) 467.259358, found 467.259602.

100 had: FTIR (CH_2Cl_2 cast) 3451 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.57 (q, $J = 7.9$ Hz, 6 H), 0.93 (t, $J = 7.9$ Hz, 9 H), 1.06-1.22 (m, 2 H), 1.75 (br s, 1 H), 1.96-2.07 (m, 2 H), 2.11 (d, $J = 2.6$ Hz, 1 H), 2.38 (dtd, $J = 7.2, 6.9, 1.0$ Hz, 2 H), 2.86 (d, $J = 2.2$ Hz, 1 H), 3.47 (td, $J = 6.9, 1.0$ Hz, 2 H), 3.80 (s, 3 H), 3.85 (br s, 1 H), 4.45 (s, 2 H), 5.21 (dd, $J = 10.8, 1.4$ Hz, 1 H), 5.31 (dd, $J = 17.9, 1.4$ Hz, 1 H), 5.45 (t, $J = 7.2$ Hz, 1 H), 6.21 (dd, $J = 17.9, 10.8$ Hz, 1 H), 6.83-6.92 (m, 2 H), 7.22-7.30 (m, 2 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 6.52 (t'), 7.00 (q'), 24.93 (t'), 26.46 (t'), 30.01 (t'), 46.06 (d'), 53.10 (d'), 55.33 (q'), 69.45 (t'), 72.66 (t'), 76.28 (d'), 86.18 (s'), 113.81 (d'), 118.22 (t'), 120.48 (d'), 129.30 (d'), 130.56 (s'), 141.01 (d'), 150.83 (s'), 159.23 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{26}\text{H}_{40}\text{NaO}_4\text{Si}$ (M + Na) 467.259358, found 467.258897.

(d'), 85.02 (s'), 113.78 (d'), 117.24 (t'), 118.65 (d'), 127.56 (d'), 127.93 (d'), 128.37 (d'), 129.27 (d'), 130.69 (s'), 138.15 (d'), 138.68 (s'), 146.50 (s'), 159.17 (s'); exact mass (HR electrospray) m/z calcd for $C_{33}H_{46}NaO_4Si$ (M + Na) 557.306309, found 557.305561.

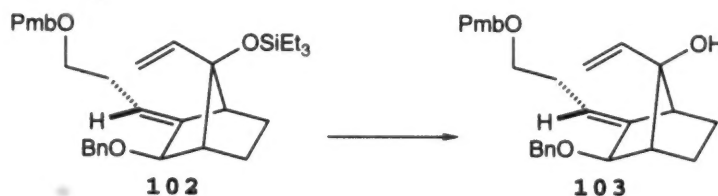
(1 α ,2 α ,3*E*,4 α ,7*R*^{*})-[[7-Ethenyl-2-[3-[(4-methoxyphenyl)methoxy]propylidene]-3-(phenylmethoxy)bicyclo[2.2.1]hept-7-yl]oxy]triethylsilane (102).



The procedure for making **83** was followed, using NaH (80% dispersion in oil, 5.2 mg, 0.17 mmol), BnBr (0.020 mL, 0.170 mmol), and **100** (16.3 mg, 0.0367 mmol) in THF (5 mL). Flash chromatography of the crude product over silica gel (1 x 10 cm), using 1:10 EtOAc-hexane, gave **102** (17.3 mg, 88%) as a pure (^1H NMR, 360 MHz), colorless oil: FTIR (CH_2Cl_2 cast) unexceptional; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.60 (q, J = 7.8 Hz, 6 H), 0.94 (t, J = 7.8 Hz, 9 H), 0.97-1.04 (m, 1 H), 1.11-1.19 (m, 1 H), 1.94-2.08 (m, 2 H), 2.21 (d, J = 3.4 Hz, 1 H), 2.38 (td, J = 7.8, 7.4 Hz, 2 H), 2.83 (br s, 1 H), 3.45 (t, J = 7.2 Hz, 2 H), 3.70 (br s, 1 H), 3.80 (s, 3 H), 4.44 (s, 2 H), 4.47 (d, J = 12.2 Hz, 1 H), 4.58 (d, J = 12.2 Hz, 1 H), 5.13 (dd, J = 10.8, 1.4 Hz, 1 H), 5.22 (dd, J = 17.6, 1.4 Hz,

1 H), 5.41 (t, $J = 7.2$ Hz, 1 H), 6.22 (dd, $J = 17.6, 10.8$ Hz, 1 H), 6.84-6.89 (m, 2 H), 7.25-7.38 (m, 7 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 6.62 (t'), 7.09 (q'), 24.90 (t'), 27.02 (t'), 29.92 (t'), 46.90 (d'), 48.57 (d'), 55.32 (q'), 69.56 (t'), 71.13 (t'), 72.52 (t'), 82.51 (d'), 86.71 (s'), 113.80 (d'), 115.97 (t'), 120.38 (d'), 127.43 (d'), 127.88 (d'), 128.34 (d'), 129.28 (d'), 130.66 (s'), 138.92 (s'), 139.92 (d'), 147.37 (s'), 159.19 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{33}\text{H}_{46}\text{NaO}_4\text{Si}$ 557.306309, found 557.306227.

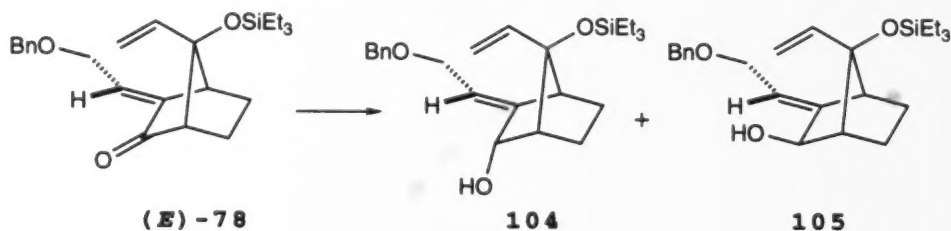
(1 α ,2 E ,3 α ,4 α ,7 R^*)-7-Ethenyl-2-[3-[(4-methoxyphenyl)methoxy]propylidene]-3-(phenylmethoxy)bicyclo-[2.2.1]heptan-7-ol (103).



The procedure for making **85** was followed, using TBAF (1.0 M in THF, 0.06 mL, 0.06 mmol) and **102** (20.0 mg, 0.0374 mmol) in THF (5 mL). Flash chromatography of the crude product over silica gel (1 x 10 cm), using 1:10 EtOAc-hexane, gave **103** (12.8 mg, 81%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3431 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.05-1.28 (m, 2 H), 1.55 (br s, 1 H), 2.00-2.16 (m, 2 H), 2.21 (d, $J = 3.4$ Hz, 1 H), 2.35 (dtd, $J = 7.3, 7.1,$

1.0 Hz, 2 H), 2.64 (d, $J = 3.0$ Hz, 1 H), 3.44 (t, $J = 7.1$ Hz, 2 H), 3.78 (br s, 1 H), 3.80 (s, 3 H), 4.43 (s, 2 H), 4.45 (d, $J = 12.0$ Hz, 1 H), 4.62 (d, $J = 12.0$ Hz, 1 H), 5.09 (dd, $J = 10.8, 1.6$ Hz, 1 H), 5.33 (dd, $J = 17.4, 1.6$ Hz, 1 H), 5.54 (td, $J = 7.3, 1.0$ Hz, 1 H), 6.56 (dd, $J = 17.4, 10.8$ Hz, 1 H), 6.82-6.88 (m, 2 H), 7.21-7.37 (m, 7 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 24.85 (t'), 26.95 (t'), 29.85 (t'), 48.63 (d'), 48.64 (d'), 55.33 (q'), 69.54 (t'), 71.35 (t'), 72.51 (t'), 83.23 (d'), 84.94 (s'), 112.66 (t'), 113.80 (d'), 121.71 (d'), 127.50 (d'), 127.80 (d'), 128.37 (d'), 129.26 (d'), 130.64 (s'), 138.78 (s'), 141.73 (d'), 146.86 (s'), 159.18 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{27}\text{H}_{32}\text{NaO}_4$ (M + Na) 443.219830, found 443.219219.

(1 α ,2 β ,3 E ,4 α ,7 S^*)-7-Ethenyl-3-[2-(phenylmethoxy)ethylidene]-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2-ol (104) and (1 α ,2 α ,3 E ,4 α ,7 S^*)-7-Ethenyl-3-[2-(phenylmethoxy)ethylidene]-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2-ol (105).

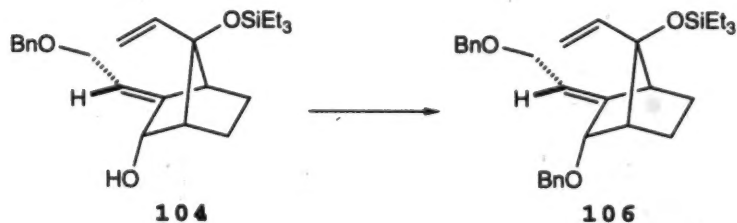


The procedure for making **81** and **82** was followed, using $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (248.6 mg, 0.668 mmol), LiBH_4 (2.0 M in THF, 0.33 mL, 0.66 mmol), **(E)-78** (221.3 mg, 0.556 mmol), and dry MeOH (30 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm), using 2:8 EtOAc-hexane, gave **104** (88.7 mg, 40%) and **105** (92.5 mg, 42%) as pure (^1H NMR, 300 and 360 MHz), colorless oils: **104** had: FTIR (CH_2Cl_2 cast) 3404 cm^{-1} ; ^1H NMR (CDCl_3 , 360 MHz) δ 0.58 (q, $J = 7.7\text{ Hz}$, 6 H), 0.94 (t, $J = 7.7\text{ Hz}$, 9 H), 1.29 (ddd, $J = 11.3, 9.0, 4.0\text{ Hz}$, 1 H), 1.67 (s, 1 H), 1.75-1.95 (m, 2 H), 2.08-2.21 (m, 2 H), 2.76 (d, $J = 4.2\text{ Hz}$, 1 H), 4.02 (ddd, $J = 11.7, 6.8, 1.2\text{ Hz}$, 1 H), 4.08 (ddd, $J = 11.7, 6.8, 1.2\text{ Hz}$, 1 H), 4.36 (br s, 1 H), 4.52 (s, 2 H), 5.17 (dd, $J = 10.8, 1.2\text{ Hz}$, 1 H), 5.24 (dd, $J = 17.7, 1.2\text{ Hz}$, 1 H), 5.59 (tdd, $J = 6.8, 1.7, 0.6\text{ Hz}$, 1 H), 5.97 (dd, $J = 17.7, 10.8\text{ Hz}$, 1 H), 7.26-7.40 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 6.52 (t'), 7.00 (q'), 18.60 (t'), 28.51 (t'), 47.91 (d'), 50.49 (d'), 67.37 (t'), 72.36 (t'), 72.38 (d'), 84.80 (s'), 117.61 (t'), 118.18 (d'), 127.65 (d'), 127.74 (d'), 128.43 (d'), 137.84 (d'), 138.47 (s'), 152.43 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{24}\text{H}_{36}\text{NaO}_3\text{Si}$ (M + Na) 423.233143, found 423.233357.

105 had: FTIR (CH_2Cl_2 cast) 3451 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.57 (q, $J = 7.8\text{ Hz}$, 6 H), 0.93 (t, $J = 7.8\text{ Hz}$, 9 H), 1.15 (dd, $J = 16.5, 9.0\text{ Hz}$, 1 H), 1.19 (dd, $J = 16.5, 8.8\text{ Hz}$, 1 H), 1.83 (s, 1 H), 2.02 (dd, $J = 9.3, 3.5\text{ Hz}$, 1 H),

2.06 (dd, $J = 9.3, 4.7$ Hz, 1 H), 2.13 (d, $J = 2.8$ Hz, 1 H), 2.88 (d, $J = 2.4$ Hz, 1 H), 3.90 (s, 1 H), 4.06 (dd, $J = 11.7, 6.6$ Hz, 1 H), 4.10 (dd, $J = 11.7, 5.9$ Hz, 1 H), 4.52 (d, $J = 11.9$ Hz, 1 H), 4.55 (d, $J = 11.9$ Hz, 1 H), 5.29 (dd, $J = 10.8, 1.2$ Hz, 1 H), 5.36 (dd, $J = 17.9, 1.2$ Hz, 1 H), 5.69 (t, $J = 6.8$ Hz, 1 H), 6.23 (dd, $J = 17.9, 10.8$ Hz, 1 H), 7.25-7.39 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 6.49 (t'), 6.97 (q'), 24.89 (t'), 26.28 (t'), 46.36 (d'), 52.73 (d'), 67.33 (t'), 72.48 (t'), 76.23 (d'), 86.17 (s'), 118.67 (t'), 120.27 (d'), 127.67 (d'), 127.75 (d'), 128.43 (d'), 138.37 (s'), 140.76 (d'), 153.28 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{24}\text{H}_{36}\text{NaO}_3\text{Si}$ ($M + \text{Na}$) 423.233143, found 423.232611.

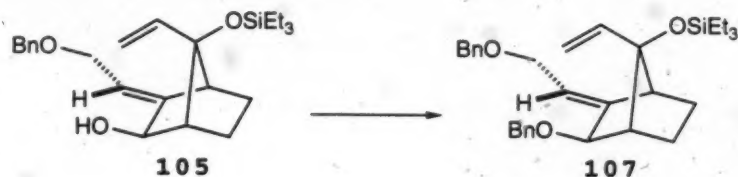
(1 α ,2 β ,3 E ,4 α ,7 S^*)-[[7-Ethenyl-2-(phenylmethoxy)-3-[2-(phenylmethoxy)ethylidene]bicyclo[2.2.1]hept-7-yl]oxy]triethylsilane (106).



The procedure for making **83** was followed, using NaH (80% dispersion in oil, 10.4 mg, 0.347 mmol), BnBr (0.040 mL, 0.340 mmol), and **104** (46.6 mg, 0.117 mmol) in THF (6 mL).

Flash chromatography of the crude product over silica gel (1 x 15 cm), using 1:10 EtOAc-hexane, gave **106** (54.0 mg, 94%) as a pure (^1H NMR, 360 MHz), colorless oil: FTIR (CH_2Cl_2 cast) unexceptional; ^1H NMR (CDCl_3 , 360 MHz) δ 0.59 (q, $J = 7.9$ Hz, 6 H), 0.95 (t, $J = 7.9$ Hz, 9 H), 1.35 (ddd, $J = 10.4$, 8.9, 3.9 Hz, 1 H), 1.77-1.96 (m, 2 H), 2.11 (dddd, $J = 11.2$, 11.2, 4.2, 4.2 Hz, 1 H), 2.28 (dd, $J = 4.2$, 4.2 Hz, 1 H), 2.76 (d, $J = 4.2$ Hz, 1 H), 4.03 (ddd, $J = 11.8$, 5.7, 1.5 Hz, 1 H), 4.09 (dd, $J = 11.8$, 7.9 Hz, 1 H), 4.14 (br s, 1 H), 4.40 (d, $J = 11.8$ Hz, 1 H), 4.52 (s, 2 H), 4.55 (d, $J = 11.8$ Hz, 1 H), 5.15 (dd, $J = 10.7$, 1.2 Hz, 1 H), 5.26 (dd, $J = 17.7$, 1.2 Hz, 1 H), 5.64 (td, $J = 7.0$, 1.0 Hz, 1 H), 5.96 (dd, $J = 17.7$, 10.7 Hz, 1 H), 7.25-7.40 (m, 10 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 6.53 (t'), 7.01 (q'), 19.05 (t'), 28.30 (t'), 47.50 (s'), 47.77 (s'), 67.42 (t'), 71.45 (t'), 72.23 (t'), 78.94 (d'), 85.00 (s'), 117.63 (t'), 119.00 (d'), 127.55 (d'), 127.62 (d'), 127.72 (d'), 127.90 (d'), 128.39 (d'), 137.94 (d'), 138.49 (s'), 138.59 (s'), 149.07 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{31}\text{H}_{42}\text{NaO}_3\text{Si}$ ($M + \text{Na}$) 513.280094, found 513.279469.

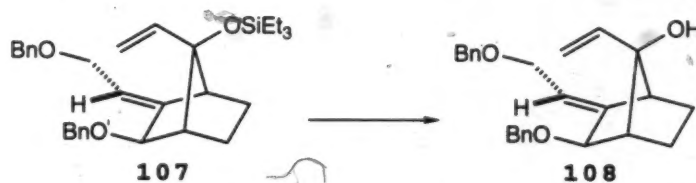
(1 α ,2 α ,3 E ,4 α ,7 S^*)-[[7-Ethenyl-2-(phenylmethoxy)-3-[2-(phenylmethoxy)ethylidene]bicyclo[2.2.1]hept-7-yl]oxy]triethylsilane (107).



The procedure for making **83** was followed, using NaH (80% dispersion in oil, 12.2 mg, 0.407 mmol), BnBr (0.05 mL, 0.4 mmol), and **105** (54.2 mg, 0.136 mmol) in THF (8 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm), using 1:10 EtOAc-hexane, gave **107** (64.0 mg, 96%) as a pure (^1H NMR, 360 MHz), colorless oil: FTIR (CH_2Cl_2 cast) unexceptional; ^1H NMR (CDCl_3 , 360 MHz) δ 0.59 (q, J = 7.9 Hz, 6 H), 0.94 (t, J = 7.9 Hz, 9 H), 1.00-1.13 (m, 1 H), 1.17-1.31 (m, 1 H), 1.96-2.13 (m, 2 H), 2.25 (d, J = 3.7 Hz, 1 H), 2.83 (d, J = 2.9 Hz, 1 H), 3.76 (s, 1 H), 4.07 (dd, J = 11.8, 6.5 Hz, 1 H), 4.10 (dd, J = 11.8, 7.1 Hz, 1 H), 4.48 (d, J = 12.2 Hz, 1 H), 4.51 (s, 2 H), 4.62 (d, J = 12.2 Hz, 1 H), 5.17 (dd, J = 10.7, 1.2 Hz, 1 H), 5.24 (dd, J = 17.7, 1.2 Hz, 1 H), 5.65 (t, J = 6.7 Hz, 1 H), 6.23 (dd, J = 17.7, 10.7 Hz, 1 H), 7.22-7.39 (m, 10 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 6.61 (t'), 7.09 (q'), 24.88 (t'), 26.86 (t'), 47.27 (d'), 48.29 (d'), 67.50 (t'), 71.31 (t'), 72.25 (t'), 82.45 (d'), 86.80 (s'), 116.32 (t'), 120.70 (d'), 127.50 (d'), 127.57 (d'), 127.75 (d'), 127.86 (d'), 128.39 (d'), 138.55 (s'), 138.73

(s'), 139.74 (d'), 149.60 (s'); exact mass (HR electrospray) m/z calcd for $C_{31}H_{42}NaO_3Si$ ($M + Na$) 513.280094, found 513.279444.

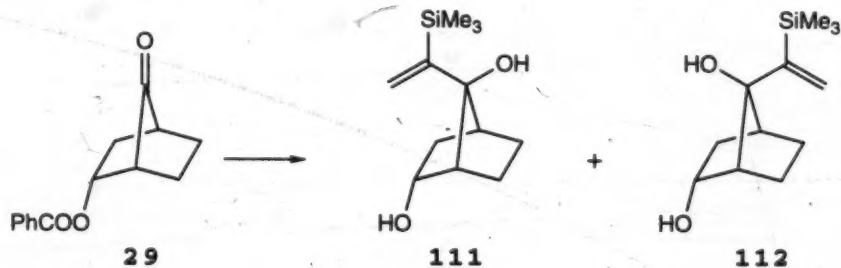
(1 α ,2 α ,3 E ,4 α ,7 S^*)-7-Ethenyl-2-(phenylmethoxy)-3-[2-(phenylmethoxy)ethylidene]bicyclo[2.2.1]heptan-7-ol (108).



The procedure for making **85** was followed, using TBAF (1.0 M in THF, 0.20 mL, 0.20 mmol) and **107** (66.8 mg, 0.136 mmol) in THF (5.0 mL). Flash chromatography of the crude product over silica gel (1 x 12 cm), using 1:10 EtOAc-hexane, gave **108** (46.8 mg, 91%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3425 cm^{-1} ; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.08–1.35 (m, 2 H), 1.61 (s, 1 H), 2.03–2.20 (m, 2 H), 2.23 (d, $J = 3.7\text{ Hz}$, 1 H), 2.66 (d, $J = 2.9\text{ Hz}$, 1 H), 3.84 (s, 1 H), 3.99–4.16 (m, 2 H), 4.47 (d, $J = 12.1\text{ Hz}$, 1 H), 4.48 (d, $J = 12.0\text{ Hz}$, 1 H), 4.52 (d, $J = 12.0\text{ Hz}$, 1 H), 4.66 (d, $J = 12.1\text{ Hz}$, 1 H), 5.14 (dd, $J = 10.9, 1.5\text{ Hz}$, 1 H), 5.36 (dd, $J = 17.4, 1.5\text{ Hz}$, 1 H), 5.76 (tdd, $J = 6.7, 1.2, 0.7\text{ Hz}$, 1 H), 6.60 (dd, $J = 17.4, 10.9\text{ Hz}$, 1 H), 7.23–7.42 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 24.79 (t'), 26.77 (t'), 48.33 (d'), 48.88 (d'), 67.29 (t'), 71.50 (t'), 72.08 (t'),

83.09 (d'), 85.02 (s'), 112.92 (t'), 121.84 (d'), 127.55 (d'), 127.59 (d'), 127.74 (d'), 127.77 (d'), 128.38 (d'), 138.43 (s'), 138.56 (s'), 141.45 (d'), 149.06 (s'); exact mass (HR electrospray) m/z calcd for $C_{25}H_{28}NaO_3Si$ ($M + Na$) 399.193615, found 399.193231.

(*Endo*, *anti*)-7-[1-(Trimethylsilyl)ethenyl]-bicyclo[2.2.1]heptane-2,7-diol (111) and (*Endo*, *syn*)-7-[1-(Trimethylsilyl)ethenyl]bicyclo[2.2.1]heptane-2,7-diol (112).



t -BuLi (1.7 M in pentane, 2.59 mL, 4.40 mmol) was added dropwise to a stirred and cooled (-78°C) solution of (1-bromoethenyl)trimethylsilane⁵⁰ (394 mg, 2.20 mmol) in THF (20.0 mL). Stirring at -78°C was continued for 2 h, and the resulting yellow solution was transferred via a cooled cannula [the cannula was placed in a rubber tube, slit lengthwise and packed with solid CO_2] to a stirred and cooled (-78°C) solution of **29**³⁰ (464 mg, 2.02 mmol) in THF (10 mL). Stirring at -78°C was continued for 3 h, and the mixture was quenched with saturated aqueous NH_4Cl (5.0 mL). The organic phase was washed with water (15 mL) and brine (15 mL), dried

and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 1:10 EtOAc-hexane, gave a mixture of the addition products (371.3 mg, 55%).

LiAlH_4 (85.0 mg, 2.24 mmol) was added in two portions to a stirred and cooled (0 °C) solution of the above mixture (371.3 mg, 1.121 mmol) in THF (12 mL). The cold bath was removed, stirring was continued for 30 min, and then water (0.1 mL) and 15% (w/v) NaOH (0.1 mL) were added successively at 0 °C. The cold bath was removed, and stirring was continued for 10 min. The mixture was filtered through a pad (2.5 x 2 cm) of Celite, and the pad was rinsed with Et₂O (20 mL). Evaporation of the combined filtrates, and flash chromatography of the residue over silica gel (1.5 x 15 cm), using 4:6 EtOAc-hexane, gave **111** (225.3 mg, 89%) and **112** (20.2 mg, 8%) as pure (¹H NMR, 360 MHz), white solids. **111** had: FTIR (CH₂Cl₂ cast) 3379 cm⁻¹; ¹H NMR (CDCl₃, 360 MHz) δ 0.19 (s, 9 H), 0.94 (dd, *J* = 12.9, 3.5 Hz, 1 H), 1.34-1.47 (m, 3 H), 1.79-1.91 (m, 1 H), 1.95-2.11 (m, 3 H), 2.14 (dd, *J* = 4.4, 4.4 Hz, 1 H), 2.29 (dd, *J* = 4.2, 4.2 Hz, 1 H), 4.13-4.22 (m, 1 H), 5.57 (d, *J* = 2.2 Hz, 1 H), 5.90 (d, *J* = 2.2 Hz, 1 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 0.62 (q'), 18.14 (t'), 28.25 (t'), 38.70 (t'), 42.84 (d'), 48.48 (d'), 69.83 (d'), 88.88 (s'), 127.25 (t'), 151.86 (s'); exact mass *m/z* calcd for C₁₂H₂₂O₂Si 226.13892, found 226.13933.

112 had: FTIR (CH₂Cl₂ cast) 3330 cm⁻¹; ¹H NMR (CDCl₃, 360 MHz) δ 0.18 (s, 9 H), 1.06 (dd, *J* = 12.7, 3.1 Hz, 1 H), 1.23-1.67 (m, 5 H), 1.84-1.96 (m, 1 H), 2.12 (dd, *J* = 4.5,

4.5 Hz, 1 H), 2.23 (dd, $J = 4.0, 4.0$ Hz, 1 H), 2.45-2.57 (m, 1 H), 4.72-4.79 (m, 1 H), 5.55 (d, $J = 2.3$ Hz, 1 H), 5.90 (d, $J = 2.3$ Hz, 1 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 0.67 (q'), 17.63 (t'), 27.63 (t'), 39.00 (t'), 42.62 (d'), 47.56 (d'), 71.77 (d'), 90.77 (s'), 126.64 (t'), 152.11 (s'); exact mass m/z calcd for $\text{C}_{12}\text{H}_{22}\text{O}_2\text{Si}$ 226.13892, found 226.13849.

The geometry of **111** was confirmed by X-ray analysis.

(Endo, anti)-7-[1-

(Trimethylsilyl)ethenyl]bicyclo[2.2.1]heptane-2,7-diol (**111**)

($\text{C}_{12}\text{H}_{22}\text{O}_2\text{Si}$) crystallizes in the orthorhombic space group

$P2_12_12$ (No. 18) with $a = 11.6446$ (3) Å, $b = 11.9457$ (6) Å, $c = 9.4735$ (3) Å, $V = 1317.79$ (9) Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.141$ g cm⁻³,

$\mu = 1.418$ mm⁻¹. X-ray diffraction data were collected on a Siemens P4/RA instrument with Cu K α radiation ($\lambda = 1.54178$ Å)

at -60 °C. The final model, with 1717 unique data used and 138 parameters varied, converged to values of $R_1 (F_o) = 0.0319$

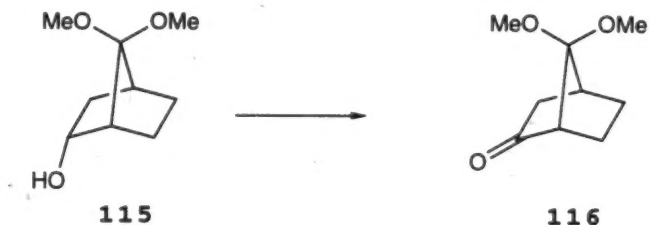
(for 1645 data with $F_o^2 > 2\sigma(F_o^2)$), and $wR_2 (F_o^2) = 0.0792$ (all

data). The absolute stereochemistry of the molecule was

established unambiguously from the X-ray data (refinement in

the opposite configuration resulted in significantly poorer residuals).

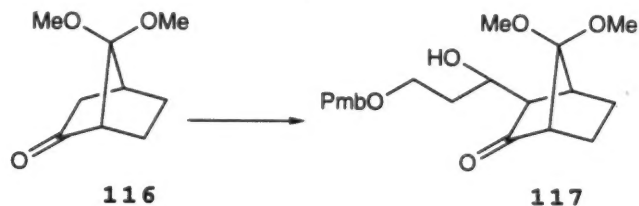
7,7-Dimethoxybicyclo[2.2.1.]heptan-2-one (116).



Compound **115**⁸ (1.49 g, 8.66 mmol) in CH_2Cl_2 (30 mL) was added rapidly to a stirred mixture of PCC (7.47 g, 34.6 mmol), NaOAc (0.570 g, 6.93 mmol) and powdered molecular sieves (3Å, 8.66 g) in CH_2Cl_2 (150 mL). Stirring was continued for 40 min, the mixture was diluted with Et_2O (80 mL) and filtered through a pad (5 x 6 cm) of silica gel. The pad was rinsed with Et_2O (150 mL) and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 2:8 EtOAc-hexane, gave **116** (1.45 g, 99%) as a pure (^1H NMR, 360 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1756 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.38-1.56 (m, 2 H), 1.92 (d, $J = 17.6\text{ Hz}$, 1 H), 1.94-2.04 (m, 2 H), 2.44 (ddd, $J = 17.6, 5.4, 1.8\text{ Hz}$, 1 H), 2.50-2.58 (m, 2 H), 3.23 (s, 3 H), 3.26 (s, 3 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 21.47 (t'), 26.12 (t'), 38.37 (d'), 44.24 (t'), 50.16 (d'), 51.06 (q'), 52.84 (q'), 111.76 (s'), 213.06 (s'); exact mass m/z calcd for $\text{C}_9\text{H}_{14}\text{O}_3$ 170.09430, found 170.09371.

(1 α ,3 β ,4 α)-7,7-Dimethoxy-3-[1-hydroxy-3-[(4-methoxyphenyl)methoxy]propyl]bicyclo[2.2.1]heptan-2-one (117).

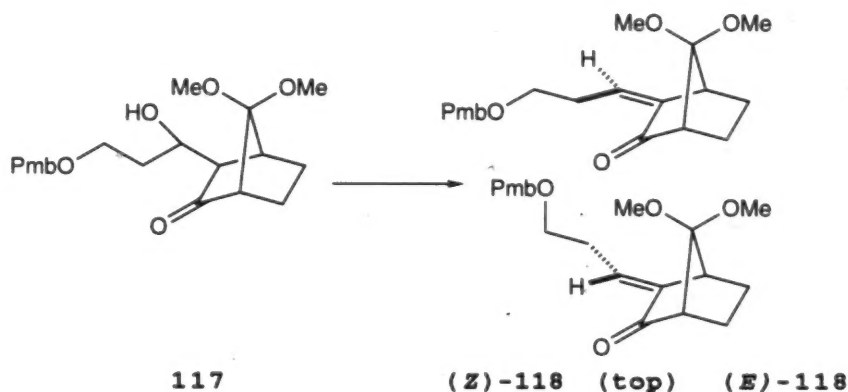
Note that the stereochemistry at C(3) is an arbitrary assignment.



The procedure for making **96** was followed, using **116** (0.260 g, 1.53 mmol) in THF (20 mL), LDA (1.67 mmol, 1.1 equiv) in THF (10 mL), and 3-[(4-methoxyphenyl)methoxy]propanal (400 mg, 2.1 mmol). Flash chromatography of the crude product over silica gel (1.2 x 15 cm), using 1:9 EtOAc-hexane, gave **117** (500 mg, 89%) as a pure (^1H NMR, 300 MHz), colorless oil. The material, which was a single isomer of unestablished stereochemistry at the two newly-created asymmetric centers, had: FTIR (CH_2Cl_2 cast) 3507, 1733 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.36-1.47 (m, 1 H), 1.48-1.58 (m, 1 H), 1.68 (dddd, $J = 13.5, 8.1, 5.7, 5.7$ Hz, 1 H), 1.84-2.10 [m, including ddd at δ 1.89 ($J = 13.5, 7.0, 2.6$ Hz, 1 H) and d at δ 2.06 ($J = 9.4$ Hz, 1 H), 4 H in all], 2.38-2.43 (m, 1 H), 2.59 (dd, $J = 4.5, 1.4$ Hz, 1 H), 3.18 (s, 3 H), 3.22 (s, 3 H), 3.55-3.72 (m, 2 H), 3.78 (s, 3 H), 3.90 (br s, 1 H), 4.10 (ddd, $J = 9.1, 8.8, 2.7$ Hz, 1 H), 4.42 (s, 2 H), 6.81-6.88 (m, 2 H), 7.49-7.27 (m, 2 H); ^{13}C NMR (CDCl_3 ,

75.5 MHz) δ 27.58 (t'), 33.37 (t'), 40.23 (t'), 45.36 (d'), 53.06 (d'), 54.17 (d'), 55.91 (q'), 57.84 (q'), 62.53 (q'), 67.58 (t'), 70.22 (d'), 73.30 (t'), 107.10 (s'), 109.28 (d'), 122.94 (d'), 124.20 (s'), 149.25 (s'), 200.53 (s'); exact mass (HR electrospray) m/z calcd for $C_{20}H_{28}NaO_6$ (M + Na) 387.178359, found 387.178555.

(3Z)-7,7-Dimethoxy-3-[3-[(4-methoxyphenyl)-methoxy]propylidene]bicyclo[2.2.1]heptan-2-one (Z)-118
and (3E)-7,7-Dimethoxy-3-[3-[(4-methoxyphenyl)-methoxy]propylidene]bicyclo[2.2.1]heptan-2-one (E)-118.



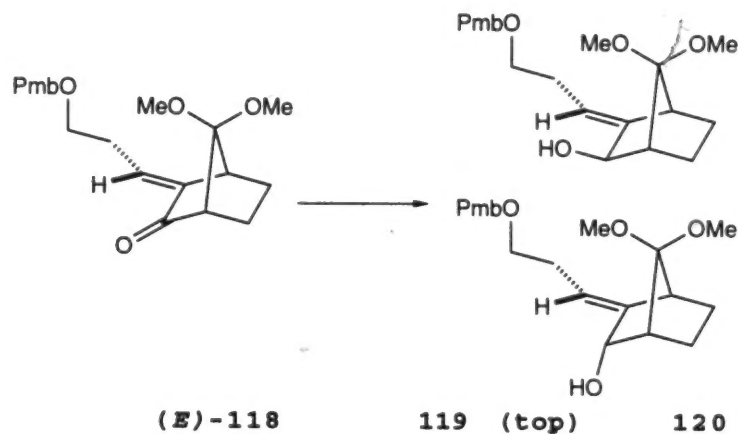
The procedure for making **(E)-97** and **(Z)-97** was followed, using **117** (1.04 g, 2.86 mmol) and Et_3N (1.52 mL, 10.6 mmol) in THF (40 mL), and $MeSO_2Cl$ (0.46 mL, 5.8 mmol) for the first step, and THF (40 mL) and DBU (0.92 mL, 6.1 mmol) for the second step. Flash chromatography of the crude product over silica gel (1.5 x 15 cm), using 1:20 EtOAc-

hexane, gave (**Z**)-118 (270 mg, 27%) and (**E**)-118 (680 mg, 69%) as pure (^1H NMR, 300 MHz), colorless oils. (**Z**)-118 had: FTIR (CH_2Cl_2 cast) 1731 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.44 (d, $J = 9.7\text{ Hz}$, 1 H), 1.50 (d, $J = 10.3\text{ Hz}$, 1 H), 1.85-2.12 (m, 2 H), 2.68 (dd, $J = 4.8, 1.9\text{ Hz}$, 1 H), 2.91 (dd, $J = 4.1, 1.5\text{ Hz}$, 1 H), 2.93 (dt, $J = 7.4, 6.3\text{ Hz}$, 2 H), 3.20 (s, 3 H), 3.24 (s, 3 H), 3.52 (t, $J = 6.3\text{ Hz}$, 2 H), 3.78 (s, 3 H), 4.41 (s, 2 H), 5.93 (t, $J = 7.4\text{ Hz}$, 1 H), 6.82-6.89 (m, 2 H), 7.20-7.27 (m, 2 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 21.22 (t'), 27.00 (t'), 28.85 (t'), 47.31 (d'), 49.80 (d'), 51.24 (d'), 54.65 (q'), 55.23 (q'), 69.00 (d'), 72.24 (d'), 110.50 (s'), 113.73 (d'), 129.20 (d'), 130.55 (s'), 133.40 (d'), 141.26 (s'), 159.13 (s'), 202.37 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{20}\text{H}_{26}\text{NaO}_5$ ($M + \text{Na}$) 369.167794, found 369.167453.

(**E**)-118 had: FTIR (CH_2Cl_2 cast) 1736 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.37-1.54 (m, 2 H), 1.90-2.12 (m, 2 H), 2.44 (dtd, $J = 7.7, 6.7, 1.0\text{ Hz}$, 2 H), 2.71 (dd, $J = 4.6, 1.7\text{ Hz}$, 1 H), 3.13-3.20 [m, including s at δ 3.16 (3 H), 4 H in all], 3.26 (s, 3 H), 3.52 (t, $J = 6.7\text{ Hz}$, 2 H), 3.78 (s, 3 H), 4.43 (s, 2 H), 6.42 (td, $J = 7.7, 0.8\text{ Hz}$, 1 H), 6.82-6.88 (m, 2 H), 7.18-7.26 (m, 2 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 21.68 (t'), 26.40 (t'), 29.69 (t'), 42.46 (d'), 49.91 (d'), 51.38 (q'), 53.07 (q'), 55.27 (q'), 68.46 (t'), 72.75 (t'), 110.93 (s'), 113.78 (d'), 127.76 (d'), 129.27 (d'), 130.23 (s'), 143.14 (s'), 159.23 (s'), 201.04 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{20}\text{H}_{26}\text{NaO}_5$ ($M + \text{Na}$) 369.167794,

found 369.167979.

(*Exo*,3*E*)-7,7-Dimethoxy-3-[3-[(4-methoxyphenyl)-methoxy]propylidene]bicyclo[2.2.1]heptan-2-ol (**119**) and (*Endo*,3*Z*)-7,7-Dimethoxy-3-[3-[(4-methoxyphenyl)-methoxy]propylidene]bicyclo[2.2.1]heptan-2-ol (**120**).



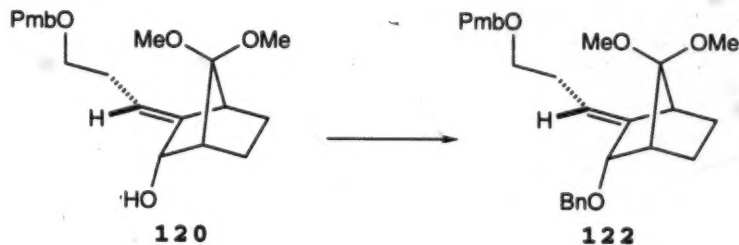
The procedure for making **81** and **82** was followed, using $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (840 mg, 2.26 mmol), LiBH_4 (2.0 M in THF, 2.25 mL, 4.50 mmol), (*E*)-**118** (650 mg, 1.88 mmol), and dry MeOH (25 mL). Flash chromatography of the crude product over silica gel (1.5 x 15 cm), using 2:8 EtOAc-hexane, gave **119** (446 mg, 68%) and **120** (127 mg, 19%) as pure (^1H NMR, 300 MHz), colorless oils: **119** had: FTIR (CH_2Cl_2 cast) 3538 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.08-1.24 (m, 2 H), 1.67-1.94 (m, 2 H), 2.18 (dd, $J = 4.8, 1.2\text{ Hz}$, 1 H), 2.36 (dt, $J = 7.0, 7.0\text{ Hz}$, 2 H), 2.84 (br s, 1 H), 2.88 (d, $J = 4.3\text{ Hz}$, 1 H), 3.20 (s, 3

H), 3.26 (s, 3 H), 3.45 (t, $J = 7.0$ Hz, 2 H), 3.78 (s, 3 H), 3.88 (br s, 1 H), 4.43 (s, 2 H), 5.59 (t, $J = 7.0$ Hz, 1 H), 6.82-6.90 (m, 2 H), 7.20-7.28 (m, 2 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 22.55 (t'), 26.16 (t'), 29.86 (t'), 42.33 (d'), 45.30 (d'), 50.32 (q'), 50.57 (q'), 55.28 (q'), 69.61 (t'), 72.58 (t'), 76.49 (d'), 113.76 (d'), 114.12 (s'), 121.36 (d'), 129.23 (d'), 130.54 (s'), 149.02 (s'), 159.18 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{20}\text{H}_{28}\text{NaO}_5$ (M + Na) 371.183444, found 371.183861.

120 had: FTIR (CH_2Cl_2 cast) 3439 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.28 (ddd, $J = 11.8, 9.7, 4.0$ Hz, 1 H), 1.56-1.70 (m, 2 H), 1.73-1.84 (m, 1 H), 1.86-1.98 (m, 1 H), 2.23-2.43 (m, 3 H), 2.83 (d, $J = 4.2$ Hz, 1 H), 3.19 (s, 3 H), 3.26 (s, 3 H), 3.46 (t, $J = 7.0$ Hz, 2 H), 3.80 (s, 3 H), 4.43 (s, 2 H), 4.59 (br d, $J = 4.3$ Hz, 1 H), 5.48 (t, $J = 7.3$ Hz, 1 H), 6.83-6.91 (m, 2 H), 7.20-7.29 (m, 2 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 17.62 (t'), 27.69 (t'), 29.70 (t'), 43.15 (d'), 44.60 (d'), 49.85 (q'), 50.88 (q'), 55.33 (q'), 69.62 (t'), 72.59 (t'), 73.02 (d'), 111.92 (s'), 113.82 (d'), 118.72 (d'), 129.32 (d'), 130.57 (s'), 149.06 (s'), 159.23 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{20}\text{H}_{28}\text{NaO}_5$ (M + Na) 371.183444, found 371.183848.

found 461.230142.

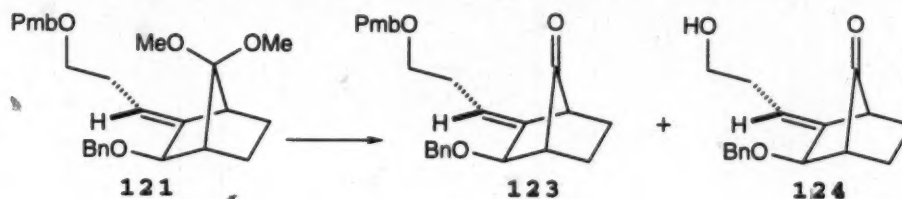
(Endo, 2E)-7,7-Dimethoxy-2-[3-[(4-methoxyphenyl)-methoxy]propylidene]-3-(phenylmethoxy)bicyclo[2.2.1]-heptane (122).



The procedure for making **83** was followed, using NaH (80% dispersion in oil, 24.1 mg, 0.830 mmol), BnBr (0.10 mL, 0.84 mmol), and **120** (126.9 mg, 0.365 mmol) in THF (20 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm), using 1:10 EtOAc-hexane, gave **122** (134.5 mg, 84%) as a pure (¹H NMR, 300 MHz), colorless oil: FTIR (CH₂Cl₂ cast) unexceptional; ¹H NMR (CDCl₃, 300 MHz) δ 1.32-1.44 (m, 1 H), 1.50-1.64 (m, 1 H), 1.80-1.98 (m, 2 H), 2.27-2.42 (m, 2 H), 2.44 (t, *J* = 4.4 Hz, 1 H), 2.84 (d, *J* = 4.2 Hz, 1 H), 3.16 (s, 3 H), 3.27 (s, 3 H), 3.46 (t, *J* = 7.2 Hz, 2 H), 3.80 (s, 3 H), 4.37 (br s, 1 H), 4.43 (d, *J* = 11.7 Hz, 1 H), 4.44 (s, 2 H), 4.55 (d, *J* = 11.7 Hz, 1 H), 5.51 (t, *J* = 7.2 Hz, 1 H), 6.82-6.90 (m, 2 H), 7.22-7.42 (m, 7 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 17.98 (t'), 27.56 (t'), 29.78 (t'), 41.42 (d'), 42.97 (d'), 49.82 (q'), 50.82 (q'), 55.30 (q'), 69.69 (t'), 71.50 (t'), 72.51 (t'), 79.80 (d'), 112.05 (s'), 113.77 (d'),

119.23 (d'), 127.62 (d'), 127.95 (d'), 128.40 (d'), 129.26 (d'), 130.66 (s'), 138.56 (s'), 145.62 (s'), 159.15 (s'); exact mass (HR electrospray) m/z calcd for $C_{27}H_{34}NaO_5$ (M + Na) 461.230394, found 461.229725.

(*Exo,2E*)-2-[3-[(4-Methoxyphenyl)methoxy]-propylidene]-3-(phenylmethoxy)bicyclo[2.2.1]heptan-7-one (**123**) and (*Exo,2E*)-2-[3-Hydroxypropylidene]-3-(phenylmethoxy)bicyclo[2.2.1]heptan-7-one (**124**).

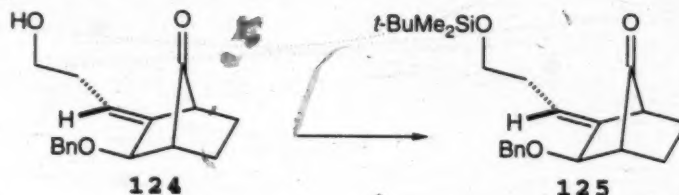


Amberlyst-15 (364 mg) was added to a solution of **121** (455 mg, 1.04 mmol) in dry acetone (35 mL). The mixture was stirred for 32 h, and the resin was filtered off. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.5 x 15 cm), using 1:9 and then 1:1 EtOAc-hexane, gave **123** (238 mg, 58%) and **124** (110 mg, 39%) as pure (^1H NMR, 300 MHz), colorless oils. **123** had: FTIR (CH_2Cl_2 cast) 1776 cm^{-1} ; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.33-1.62 (m, 2 H), 1.85-2.00 (m, 2 H), 2.34 (d, $J = 4.3\text{ Hz}$, 1 H), 2.38 (dt, $J = 7.1, 6.7\text{ Hz}$, 2 H), 2.77 (dd, $J = 2.6, 1.0\text{ Hz}$, 1 H), 3.49 (t, $J = 6.7\text{ Hz}$, 2 H), 3.80 (s, 3 H), 4.02 (s, 1 H), 4.45

(s, 2 H), 4.53 (dd, $J = 11.4$ Hz, 1 H), 4.57 (dd, $J = 11.4$ Hz, 1 H), 5.65 (t, $J = 7.1$ Hz, 1 H), 6.83-6.90 (m, 2 H), 7.21-7.38 (m, 7 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 18.29 (t'), 24.34 (t'), 29.81 (t'), 43.44 (d'), 44.97 (d'), 55.28 (q'), 69.14 (t'), 70.07 (t'), 72.62 (t'), 80.64 (d'), 113.79 (d'), 125.43 (d'), 127.61 (d'), 127.73 (d'), 128.40 (d'), 129.24 (d'), 130.41 (s'), 138.05 (s'), 139.64 (s'), 159.21 (s'), 212.30 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{25}\text{H}_{28}\text{NaO}_4$ (M + Na) 414.188529, found 415.188332.

124 had: FTIR (CH_2Cl_2 cast) 3424, 1775 cm^{-1} ; ^1H NMR (CD_2Cl_2 , 300 MHz) δ 1.38-1.62 (m, 2 H), 1.76 (br s, 1 H), 1.87-2.02 (m, 2 H), 2.26-2.36 [m, including dt at δ 2.31 ($J = 7.2, 6.8$ Hz, 2 H), 3 H in all], 2.76 (dd, $J = 2.2, 1.0$ Hz, 1 H), 3.56-3.68 (m, 2 H), 4.05 (s, 1 H), 4.52 (d, $J = 11.8$ Hz, 1 H), 4.57 (d, $J = 11.8$ Hz, 1 H), 5.63 (t, $J = 7.2$ Hz, 1 H), 7.24-7.39 (m, 5 H); ^{13}C NMR (CD_2Cl_2 , 75.5 MHz) δ 18.61 (t'), 24.79 (t'), 33.05 (t'), 43.88 (d'), 45.36 (d'), 62.20 (t'), 70.75 (t'), 81.43 (d'), 125.42 (d'), 127.96 (d'), 128.15 (d'), 128.71 (d'), 138.62 (s'), 140.94 (s'), 212.35 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{17}\text{H}_{20}\text{NaO}_3$ (M + Na) 295.131014, found 295.131260.

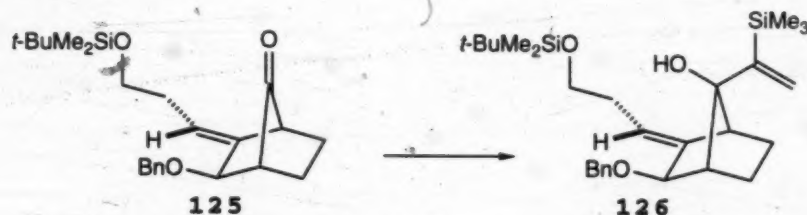
(Exo,2E)-2-[[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]propylidene]-3-(phenylmethoxy)bicyclo[2.2.1]-heptan-7-one (125).



$t\text{-BuMe}_2\text{SiCl}$ (20.0 mg, 0.133 mmol) was added to a stirred solution of **124** (18.1 mg, 0.0665 mmol) and imidazole (13.6 mg, 0.200 mmol) in CH_2Cl_2 (2.0 mL). Stirring was continued for 5 h, the mixture was diluted with Et_2O (15 mL), washed with water (10 mL) and brine (10 mL), dried and evaporated. Flash chromatography of the residue over silica gel (1 x 10 cm), using 1:10 EtOAc -hexane, gave **125** (19.8 mg, 77%) as pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1778 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.06 (s, 6 H), 0.88 (s, 9 H), 1.34-1.61 (m, 2 H), 1.85-2.02 (m, 2 H), 2.30 (dt, $J = 7.1$, 6.8 Hz, 2 H), 2.36 (d, $J = 5.2$ Hz, 1 H), 2.77 (br s, 1 H), 3.66 (td, $J = 6.8$, 1.5 Hz, 2 H), 4.01 (s, 1 H), 4.54 (d, $J = 12.1$ Hz, 1 H), 4.58 (d, $J = 12.1$ Hz, 1 H), 5.63 (t, $J = 7.1$ Hz, 1 H), 7.23-7.39 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ -5.25 (q'), 18.32 (s'), 24.47 (t'), 25.99 (q'), 32.89 (t'), 43.48 (d'), 44.99 (d'), 62.54 (t'), 70.07 (t'), 80.68 (d'), 125.73 (d'), 127.63 (d'), 127.74 (d'), 128.42 (d'), 138.10 (s'), 139.52 (s'), 212.88 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{23}\text{H}_{34}\text{NaO}_3\text{Si}$ ($M + \text{Na}$) 409.217493, found

409.217536.

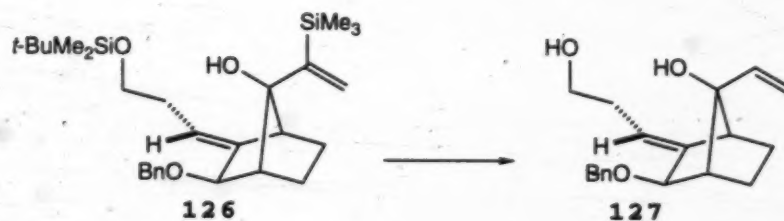
(1 α ,2 E ,3 α ,4 α ,7 S^*)-2-[[[(1,1-Dimethylethyl)-dimethylsilyl]oxy]propylidene]-3-(phenylmethoxy)-7-[1-(trimethylsilyl)ethenyl]bicyclo[2.2.1]heptan-7-ol (126).



t-BuLi (1.7 M in pentane, 0.57 mL, 0.97 mmol) was added dropwise to a stirred and cooled (-78°C) solution of (1-bromoethenyl)trimethylsilane⁵⁰ (86.2 mg, 0.48 mmol) in THF (3 mL). Stirring was continued at -78°C for 2 h, and a solution of **125** (22.4 mg, 0.058 mmol) in THF (3 mL) was added dropwise to the resulting yellow solution. Stirring was continued for 1.5 h at -78 °C, and the mixture was quenched with saturated aqueous NH₄Cl, washed with water and brine, dried and evaporated. Flash chromatography of the residue over silica gel (1 x 12 cm), using 1:10 EtOAc-hexane, gave **126** (24.3 mg, 86%) as a pure (¹H NMR, 400 MHz), colorless oil: FTIR (CH₂Cl₂ cast) 3474 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.06 (s, 6 H), 0.20 (s, 9 H), 0.89 (s, 9 H), 0.92-1.06 (m, 1 H), 1.08-1.17 (m, 1 H), 1.59-1.75 (m, 2 H), 2.36 (dt, *J* = 7.1, 7.0 Hz, 2 H), 2.48 (d, *J* = 3.9 Hz, 1 H), 2.56 (br s, 1 H), 3.58-3.72 (m, 2 H), 3.94 (s, 1 H), 4.20 (s, 1 H), 4.58 (d, *J* = 11.8 Hz, 1 H),

4.73 (d, $J = 11.8$ Hz, 1 H), 5.60 (d, $J = 2.1$ Hz, 1 H), 5.73 (t, $J = 7.1$ Hz, 1 H), 5.90 (d, $J = 2.1$ Hz, 1 H), 7.27-7.41 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ -5.17 (q'), 0.80 (q'), 18.45 (s'), 22.46 (t'), 25.95 (t') 26.04 (q'), 33.19 (t'), 43.59 (d'), 46.99 (d'), 63.03 (t'), 71.21 (t') 84.56 (d'), 89.74 (s'), 124.62 (d'), 126.30 (t'), 127.76 (d'), 127.85 (d'), 128.47 (d'), 137.92 (s'), 146.68 (s'), 150.66 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{28}\text{H}_{46}\text{NaO}_3\text{Si}_2$ ($M + \text{Na}$) 509.288322, found 509.287500.

(1 α ,2 E ,3 α ,4 α ,7 S^*)-7-Ethylidene-2-[3-Hydroxypropylidene]-3-(phenylmethoxy)bicyclo[2.2.1]heptan-7-ol (127).

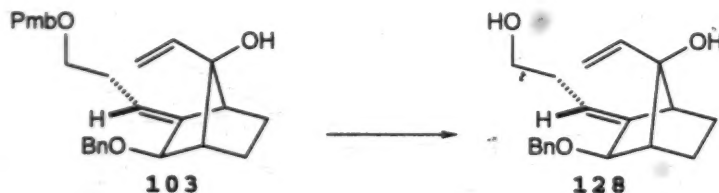


The following attempt at an anionic oxy-Cope rearrangement was made before the stereochemistry of **126** was shown to be opposite to what we required. The product of the reaction (**127**) was identified by comparison with material made from **103** (see following experiment).

126 (24.3 mg, 0.0500 mmol) in THF (2 mL) was added dropwise to a stirred suspension of KH [35% dispersion in mineral oil, 13.4 mg, washed with pentane (3 x 2 mL), 0.117 mmol] and 18-crown-6 (26.4 mg, 0.100 mmol) in THF (2 mL).

Stirring was continued for 12 h, the mixture was quenched with saturated aqueous NH_4Cl , washed with water and brine, dried and evaporated. Flash chromatography of the residue over silica gel (1 x 12 cm), using 4:6 EtOAc-hexane, gave **127** (11.2 mg, 74%) as a pure (^1H NMR, 360 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3453 cm^{-1} ; ^1H NMR (CDCl_3 , 360 MHz) δ 1.03-1.29 (m, 2 H), 1.75-1.99 (m, 2 H), 2.25 (d, $J = 3.2\text{ Hz}$, 1 H), 2.28-2.48 (m, 2 H), 2.86 (d, $J = 2.4\text{ Hz}$, 1 H), 3.67 (td, $J = 6.4, 1.9\text{ Hz}$, 2 H), 3.95 (s, 1 H), 4.58 (d, $J = 11.9\text{ Hz}$, 1 H), 4.74 (d, $J = 11.9\text{ Hz}$, 1 H), 5.26 (dd, $J = 10.8, 1.9\text{ Hz}$, 1 H), 5.54 (d, $J = 17.2, 1.9\text{ Hz}$, 1 H), 5.72 (t, $J = 7.6\text{ Hz}$, 1 H), 6.11 (dd, $J = 17.2, 10.8\text{ Hz}$, 1 H), 7.28-7.44 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 22.31 (t'), 25.73 (t'), 32.84 (t'), 45.78 (d'), 48.80 (d'), 62.20 (t'), 71.37 (t'), 84.36 (d'), 85.80 (s'), 116.36 (t'), 123.90 (d'), 127.91 (d'), 128.55 (d'), 136.72 (d'), 137.68 (s'), 148.49 (s'), mass (electrospray) m/z calcd for $\text{C}_{19}\text{H}_{24}\text{NaO}_3$ ($M + \text{Na}$) 323.2, found 323.1.

(1 α ,2 E ,3 α ,4 α ,7 R^*)-7-Ethylidene-2-[3-Hydroxypropylidene]-3-(phenylmethoxy)bicyclo[2.2.1]-heptan-7-ol (128).

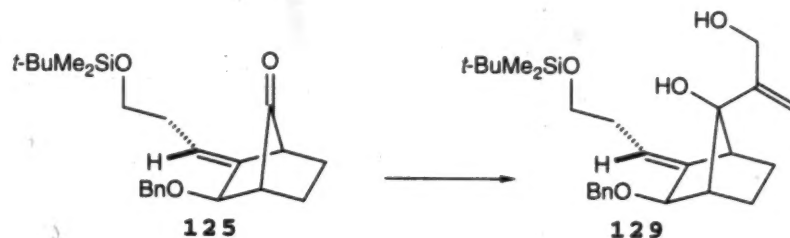


The following experiment was done in order to obtain a

sample for comparison with the product of the previous experiment. The comparison served to establish the stereochemistry of **127**.

DDQ (4.4 mg, 0.019 mmol) was added to a stirred mixture of **103** (5.4 mg, 0.013 mmol) in CH_2Cl_2 (2 mL) and water (0.1 mL). Stirring was continued for 3 h, and the mixture was then washed with saturated aqueous NaHCO_3 (1 mL), water (1 mL) and brine (1 mL), dried and evaporated. Flash chromatography of the residue over silica gel (0.5 x 5 cm), using 4:6 EtOAc-hexane, gave **128** (2.7 mg, 70%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3363 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) 1.08-1.20 (m, 1 H), 1.20-1.37 (m, 2 H), 2.06-2.21 (m, 2 H), 2.23 (d, $J = 3.2\text{ Hz}$, 1 H), 2.34 (dtd, $J = 7.1, 6.9, 1.6\text{ Hz}$, 2 H), 2.69 (d, $J = 2.4\text{ Hz}$, 1 H), 3.65 (t, $J = 6.9\text{ Hz}$, 2 H), 3.82 (br s, 1 H), 4.46 (d, $J = 11.8\text{ Hz}$, 1 H), 4.64 (d, $J = 11.8\text{ Hz}$, 1 H), 5.13 (dd, $J = 10.8, 1.9\text{ Hz}$, 1 H), 5.37 (dd, $J = 17.3, 1.9\text{ Hz}$, 1 H), 5.52 (t, $J = 7.1\text{ Hz}$, 1 H), 6.58 (dd, $J = 17.3, 10.8\text{ Hz}$, 1 H), 7.27-7.41 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) 24.86 (t'), 27.06 (t'), 32.84 (t'), 48.44 (d'), 48.77 (d'), 62.34 (t'), 71.49 (t'), 83.26 (d'), 85.06 (s'), 113.11 (t'), 121.17 (d'), 127.61 (d'), 127.87 (d'), 128.43 (d'), 138.64 (s'), 141.54 (d'), 148.33 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{19}\text{H}_{24}\text{NaO}_3$ ($M + \text{Na}$) 323.162315, found 323.162374.

(1 α ,2 E ,3 α ,4 α ,7 S^*)-2-[[[(1,1-Dimethylethyl)-dimethylsilyl]oxy]propylidene]-7-[1-(hydroxymethyl)-ethenyl]-3-(phenylmethoxy)bicyclo[2.2.1]heptan-7-ol (129).



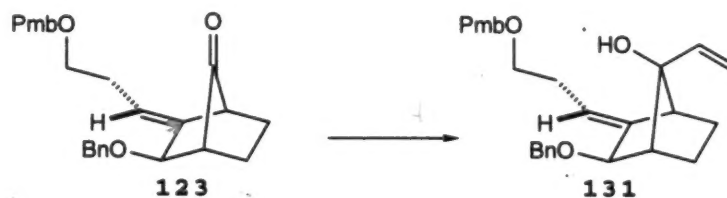
The following experiment was done before we had established that the facial selectivity for carbanion attack at the ketone carbonyl occurs in the undesired sense in more elaborate structures than **29**. The stereochemistry of **129** is tentatively assigned as shown, and this assignment is consistent with the failure of the derived **130** to undergo oxy-Cope rearrangement.

MeMgBr (3.0 M in Et₂O, 0.51 mL, 1.55 mmol) was added to a stirred and cooled (-78 °C) solution of 2-bromopropen-1-ol⁵² (202.2 mg, 1.48 mmol) in THF (10 mL). Stirring was continued for 40 min. *t*-BuLi (1.7 M in pentane, 1.82 mL, 3.10 mmol) then was added dropwise over 30 min, and stirring was continued for 2 h. **125** (39.0 mg, 0.100 mmol) in THF (2 mL) was added dropwise to the resulting solution, and stirring

was continued for 2 h. The mixture was quenched with saturated aqueous NH_4Cl , washed with water and brine, dried and evaporated. Flash chromatography of the residue over silica gel (1-x 15 cm), using 4:6 EtOAc-hexane, gave **129** (20.0 mg, 44%) as a pure (^1H NMR, 400 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3442 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 0.06 (s, 6 H), 0.89 (s, 9 H), 1.00-1.08 (m, 1 H), 1.13-1.20 (m, 1 H), 1.63-1.78 (m, 2 H), 2.37 (td, $J = 7.2, 6.7\text{ Hz}$, 2 H), 2.53 (d, $J = 4.2\text{ Hz}$, 1 H), 3.07 (br s, 1 H), 3.60-3.72 (m, 2 H), 3.98 (s, 1 H), 4.28 (d, $J = 13.0\text{ Hz}$, 1 H), 4.32 (d, $J = 13.0\text{ Hz}$, 1 H), 4.62 (d, $J = 11.8\text{ Hz}$, 1 H), 4.73 (d, $J = 11.8\text{ Hz}$, 1 H), 5.26 (d, $J = 0.9\text{ Hz}$, 1 H), 5.35 (d, $J = 0.9\text{ Hz}$, 1 H), 5.77 (t, $J = 7.2\text{ Hz}$, 1 H), 7.24-7.41 (m, 5 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ -5.21 (q'), 18.43 (s'), 22.36 (t'), 26.01 (q'), 26.11 (t'), 33.15 (t'), 43.41 (d'), 46.48 (d'), 62.86 (t'), 64.86 (t'), 71.21 (t'), 84.45 (d'), 88.57 (s'), 114.41 (t'), 124.68 (d'), 125.88 (d'), 127.90 (d'), 128.55 (d'), 137.62 (s'), 145.72 (s'), 145.93 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{26}\text{H}_{40}\text{NaO}_4\text{Si}$ ($M + \text{Na}$) 467.259358, found 467.259198.

5.25 (s, 2 H), 5.61 (m, $J = 7.1$ Hz, 1 H), 7.20-7.42 (m, 5 H); ^{13}C NMR (CDCl_3 , 125 MHz) δ -5.12 (q'), 18.48 (s'), 20.51 (s'), 21.02 (s'), 24.18 (t'), 25.59 (t'), 26.07 (q'), 27.18 (q'), 27.28 (q'), 33.33 (t'), 44.80 (d'), 47.09 (d'), 63.22 (t'), 68.70 (t'), 71.39 (t'), 85.58 (d'), 89.10 (s'), 115.23 (t'), 120.70 (d'), 127.01 (d'), 127.44 (d'), 128.05 (d'), 139.53 (s'), 145.47 (s'), 148.45 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{34}\text{H}_{56}\text{NaO}_4\text{Si}_2$ ($M + \text{Na}$) 607.361487, found 607.361436.

(1 α ,2 E ,3 α ,4 α ,7 S^*)-7-Ethenyl-2-[3-[(4-methoxyphenyl)methoxy]propylidene]-3-(phenylmethoxy)bicyclo-[2.2.1]heptan-7-ol (131).

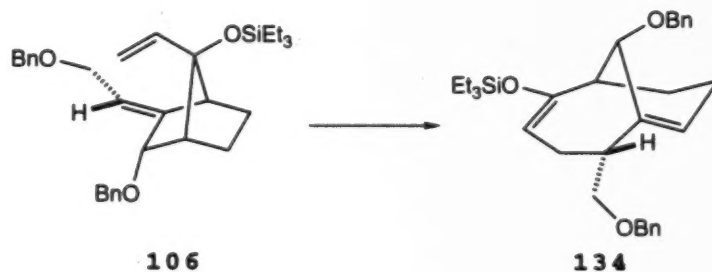


The stereochemistry of **131** was confirmed by spectroscopic comparison with **103** (see above).

Vinylmagnesium bromide (1 M, 0.20 mL, 0.20 mmol) was added dropwise to a stirred solution of **123** (20.0 mg, 0.052 mmol) in PhMe (5 mL). Stirring was continued for 48 h, the mixture was diluted with Et_2O (10 mL) and quenched with saturated aqueous NH_4Cl . The organic phase was washed with water and brine, dried and evaporated. Flash chromatography of the residue over silica gel (1 x 12 cm), using 1:20 EtOAc-

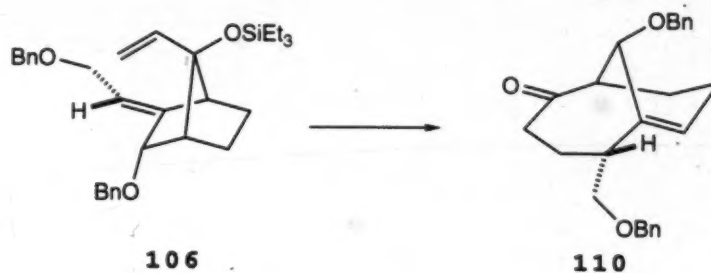
hexane, gave **131** (17.1 mg, 80%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR 3475 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.02-1.24 (m, 2 H), 1.72-1.88 (m, 2 H), 2.24 (d, $J = 3.3\text{ Hz}$, 1 H), 2.42 (dt, $J = 7.2, 7.0\text{ Hz}$, 2 H), 2.78 (d, $J = 2.5\text{ Hz}$, 1 H), 3.47 (t, $J = 7.0\text{ Hz}$, 2 H), 3.79 (s, 3 H), 3.93 (s, 1 H), 4.32 (br s, 1 H), 4.44 (s, 2 H), 4.58 (d, $J = 11.9\text{ Hz}$, 1 H), 4.72 (d, $J = 11.9\text{ Hz}$, 1 H), 5.26 (dd, $J = 10.8, 2.0\text{ Hz}$, 1 H), 5.53 (dd, $J = 17.2, 2.0\text{ Hz}$, 1 H), 5.74 (t, $J = 7.2\text{ Hz}$, 1 H), 6.12 (dd, $J = 17.2, 10.8\text{ Hz}$), 6.82-6.89 (m, 2 H), 7.22-7.38 (m, 7 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 22.25 (t'), 25.94 (t'), 30.04 (t'), 45.77 (d'), 48.84 (d'), 55.33 (q'), 69.57 (t'), 71.18 (t'), 72.56 (t'), 84.56 (d'), 85.82 (s'), 113.82 (d'), 116.23 (t'), 124.67 (d'), 127.83 (d'), 127.88 (d'), 128.51 (d'), 129.28 (d'), 130.63 (s'), 136.93 (d'), 137.80 (s'), 146.91 (s'), 159.20 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{27}\text{H}_{32}\text{NaO}_4$ (M + Na) 443.219830; found 443.219938.

(1*R,5*R**,10*S**)-[[10-(Phenylmethoxy)-5-[(phenylmethoxy)methyl]bicyclo[4.3.1]deca-2,6-dien-2-yl]oxy]-triethylsilane (134).**



A solution of **106** (22.0 mg, 0.0449 mmol) in degassed (by three freeze-thaw cycles, using a temperature of -78°C and an oil-pump vacuum) 1,2-dichlorobenzene (4 mL) was refluxed for 10 days under a slight static pressure of Ar. The solution was cooled and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:20 EtOAc-hexane, gave **134** [12.1 mg, 86% after correction for recovered starting material (8.0 mg, 36%)], as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) unexceptional; ^1H NMR (CDCl_3 , 300 MHz) δ 0.61 (q, $J = 7.9$ Hz, 6 H), 0.94 (t, $J = 7.9$ Hz, 9 H), 1.66-1.80 (m, 1 H), 1.84-1.99 (m, 1 H), 1.99-2.20 (m, 2 H), 2.43-2.66 (m, 2 H), 2.82-3.00 (m, 2 H), 3.31 (dd, $J = 8.9$, 8.9 Hz, 1), 3.69 (dd, $J = 8.9$, 5.4 Hz, 1 H), 4.38 (d, $J = 11.5$ Hz, 1 H), 4.46-4.60 (m, 5 H), 7.20-7.40 (m, 10 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 5.13 (t'), 6.81 (q'), 20.67 (t'), 22.03 (t'), 25.30 (t'), 42.38 (d'), 46.17 (d'), 70.03 (t'), 71.41 (t'), 73.20 (t'), 74.72 (d'), 101.82 (d'), 124.10 (d'), 127.44 (d'), 127.62 (d'), 127.74 (d'), 127.79 (d'), 128.36 (d'), 128.43 (d'), 138.56 (d'), 138.89 (d'), 141.61 (d'), 155.97 (d'); exact mass (HR electrospray) m/z calcd for $\text{C}_{31}\text{H}_{43}\text{O}_3\text{Si}$ (M + H) 491.298149, found 491.298051.

(1*R**,5*R**,10*S**)-10-(Phenylmethoxy)-5-[(phenylmethoxy)methyl]bicyclo[4.3.1]dec-6-ene-2-one (110).

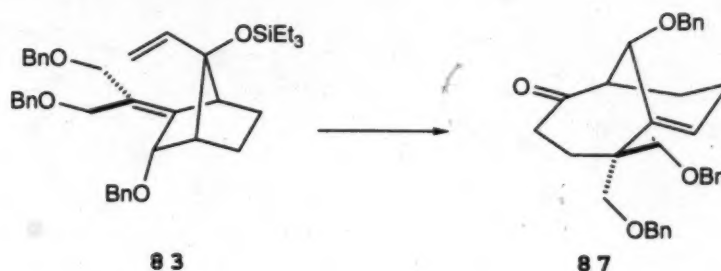


A solution of **106** (11.4 mg, 0.0232 mmol) in anhydrous 1-methyl-2-pyrrolidinone (2.5 mL) was refluxed for 24 h under a slight static pressure of Ar. The solution was cooled to room temperature, diluted with Et₂O (10 mL), washed with water (10 mL) and brine (5 mL), dried and evaporated. Flash chromatography of the residue over silica gel (1 x 12 cm), using 2:8 EtOAc-hexane, gave **110** [4.6 mg, 68% after correction for recovered starting material (2.6 mg, 23%)], as a pure (¹H NMR, 360 MHz), colorless oil: FTIR (CH₂Cl₂ cast) 1702 cm⁻¹; ¹H NMR (CDCl₃, 360 MHz) δ 1.09-1.24 (m, 1 H), 1.92-2.08 (m, 2 H), 2.13-2.26 (m, 2 H), 2.28-2.43 (m, 2 H), 2.60-2.76 (m, 2 H), 2.89 (dd, *J* = 6.7, 4.6 Hz, 1 H), 3.47 (dd, *J* = 9.2, 7.4 Hz, 1 H), 3.65 (dd, *J* = 9.2, 6.4 Hz, 1 H), 4.43 (d, *J* = 11.6 Hz, 1 H), 4.53 (s, 2 H), 4.55 (br s, 1 H), 4.56 (d, *J* = 11.6 Hz, 1 H), 5.60 (br d, *J* = 7.9 Hz, 1 H), 7.22-7.40 (m, 10 H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 18.19 (t'), 20.45 (t'), 37.76 (t'), 41.59 (t'), 45.57 (d'), 51.82 (d'), 70.31 (t'), 70.86 (t'), 73.31 (t'), 78.00 (d'), 125.05 (d'), 127.59 (d'), 127.68 (d'), 127.85 (d'), 128.44 (d'), 138.41 (s'), 143.93

(s'), 212.51 (s'); exact mass (HR electrospray) m/z calcd for $C_{25}H_{28}NaO_3$ ($M + Na$) 399.193615, found 399.193518.

(1*R**,10*S**)-5,5-Bis[(phenylmethoxy)methyl]-10-(phenylmethoxy)bicyclo[4.3.1]dec-6-ene-2-one (87).

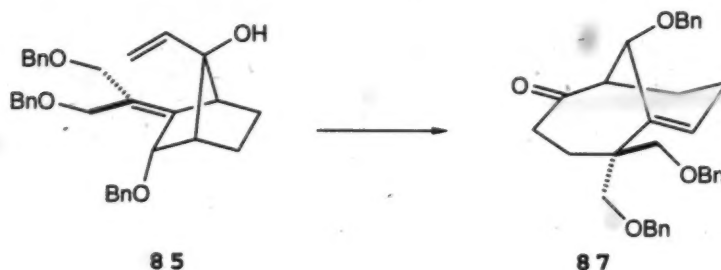
(a) starting from 83.



A solution of **83** (10.3 mg, 0.0169 mmol) in anhydrous degassed (by three freeze-thaw cycles, using a temperature of $-78\text{ }^{\circ}\text{C}$ and an oil-pump vacuum) 1-methyl-2-pyrrolidinone (4 mL) was refluxed for 4 days. The solution was cooled to room temperature, diluted with Et_2O (10 mL), washed with water (10 mL) and brine (5 mL), dried and evaporated. Flash chromatography of the residue over silica gel (1 x 12 cm), using 2:8 EtOAc-hexane, gave **87** [4.0 mg, 96% after correction for recovered starting material (5.2 mg, 50%)], as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1701 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.57–1.76 (m, 3 H), 2.01–2.18 (m, 2 H), 2.18–2.34 (m, 1 H), 2.34–2.61 (m, 2 H), 3.08 (ddd, $J = 8.7, 3.8, 1.9\text{ Hz}$, 1 H), 3.53 (d, $J = 8.8\text{ Hz}$, 1 H), 3.71 (s, 2 H), 3.76 (d, $J = 8.8\text{ Hz}$, 1 H), 4.38 (d, $J = 11.7\text{ Hz}$, 1 H), 4.46–4.59 (m, 5 H), 4.72 (dd, $J = 3.8, 1.6\text{ Hz}$, 1 H), 5.90

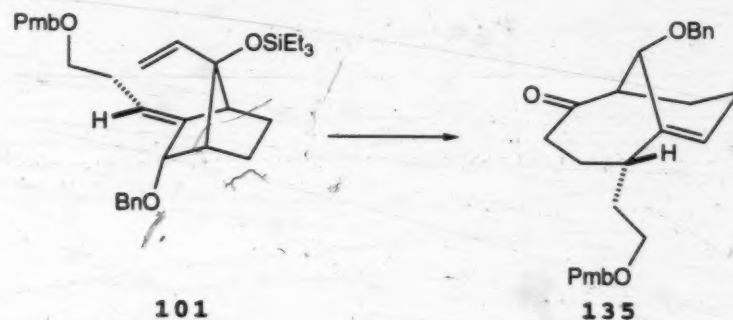
(ddd, $J = 8.3, 3.4, 1.6$ Hz, 1 H), 7.19–7.37 (m, 15 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 20.76 (t'), 21.91 (t'), 31.42 (t'), 38.66 (t'), 47.30 (s'), 52.65 (d'), 70.00 (t'), 70.67 (t'), 70.90 (t'), 71.20 (d'), 73.42 (t'), 73.54 (t'), 127.43 (d'), 127.48 (d'), 127.57 (d'), 127.61 (d'), 127.70 (d'), 128.38 (d'), 128.83 (d'), 138.32 (s'), 138.54 (s'), 138.78 (s'), 142.09 (s'), 212.93 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{33}\text{H}_{36}\text{NaO}_4$ ($M + \text{Na}$) 519.251130, found 519.251773.

(b) starting from **85**.



A solution of **85** (9.1 mg, 0.018 mmol) in anhydrous degassed (by three freeze-thaw cycles, using a temperature of -78 °C and an oil-pump vacuum) 1-methyl-2-pyrrolidinone (4 mL) was refluxed for 4 days. The solution was cooled to room temperature, diluted with Et_2O (10 mL), washed with water (10 mL) and brine (5 mL), dried and evaporated. Flash chromatography of the residue over silica gel (1 x 12 cm), using 2:8 EtOAc-hexane, gave **87** [1.8 mg, 30% after correction for recovered starting material (3.0 mg, 33%)]; as a pure (^1H NMR, 300 MHz), colorless oil, which was identified by comparison of its ^1H NMR spectrum with that of material obtained from **83** in the previous experiment.

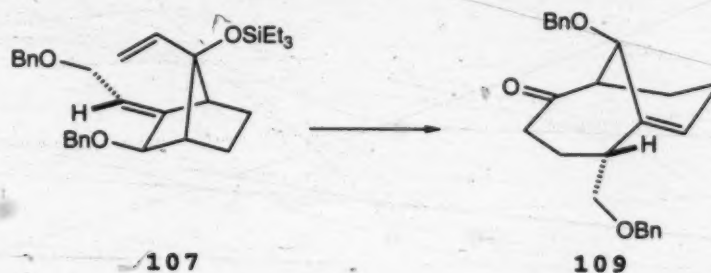
(1*R**,5*S**,10*S**)-5-[2-[(4-Methoxyphenyl)methoxy]-ethyl]-10-(phenylmethoxy)bicyclo[4.3.1]dec-6-ene-2-one (135).



A solution of **101** (5.4 mg, 0.010 mmol) in anhydrous degassed (by three freeze-thaw cycles, using a temperature of -78°C and an oil-pump vacuum) 1-methyl-2-pyrrolidinone (2.5 mL) was refluxed for 3 days. The solution was cooled to room temperature, diluted with Et_2O (10 mL), washed with water (10 mL) and brine (5 mL), dried and evaporated. Flash chromatography of the residue over silica gel (1 x 10 cm), using 2:8 EtOAc-hexane, gave **135** (3.5 mg, 83%), as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1702 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.06-1.22 (m, 1 H), 1.68-1.90 (m, 2 H), 1.90-2.11 (m, 3 H), 2.14-2.46 (m, 3 H), 2.50-2.64 (m, 1 H), 2.71 (ddd, $J = 13.9, 11.8, 3.3\text{ Hz}$, 1 H), 2.87 (dd, $J = 6.6, 4.6\text{ Hz}$, 1 H), 3.47-3.58 (m, 2 H), 3.78 (s, 3 H), 4.36 (d, $J = 11.5\text{ Hz}$, 1 H), 4.42 (s, 2 H), 4.49 (d, $J = 11.5\text{ Hz}$, 1 H), 4.56 (d, $J = 4.4\text{ Hz}$, 1 H), 5.66 (br d, $J = 7.6\text{ Hz}$, 1 H), 6.81-6.98 (m, 2 H), 7.18-7.38 (m, 7 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 17.97 (t'), 20.34 (t'), 31.42 (t'), 41.00 (t'), 41.97

(t'), 42.04 (d'), 51.71 (d'), 55.23 (q'), 67.89 (t'), 70.11 (t'), 72.73 (t'), 78.26 (d'), 113.75 (d'), 124.36 (d'), 127.58 (d'), 127.71 (d'), 128.39 (d'), 129.25 (d'), 130.43 (s'), 138.39 (s'), 145.39 (s'), 159.16 (s'), 212.62 (s'); exact mass (HR electrospray) m/z calcd for $C_{27}H_{32}NaO_4$ ($M + Na$) 443.219830, found 443.220395.

(1R*,5R*,10R*)-10-(Phenylmethoxy)-5-[(phenylmethoxy)methyl]bicyclo[4.3.1]dec-6-ene-2-one (109).



A solution of **107** (10.3 mg, 0.0021 mmol) in anhydrous degassed (by three freeze-thaw cycles, using a temperature of -78°C and an oil-pump vacuum) 1-methyl-2-pyrrolidinone (4 mL) was refluxed for 3 days. The solution was cooled to room temperature, diluted with Et_2O (10 mL), washed with water (10 mL) and brine (5 mL), dried and evaporated. Flash chromatography of the residue over silica gel (1 x 10 cm), using 2:8 EtOAc -hexane, gave **109** (6.9 mg, 86%), as a pure (^1H NMR, 360 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1696 cm^{-1} ; ^1H NMR (CDCl_3 , 360 MHz) δ 1.08-1.22 (m, 1 H), 1.80-1.96 (m, 2 H), 1.98-2.23 (m, 3 H), 2.30 (ddd, $J = 11.5, 6.0, 2.8\text{ Hz}$, 1 H), 2.79-2.85 (m, 1 H), 3.20-3.32 (m, 2 H), 3.49 (dd, $J =$

9.2, 7.2 Hz, 1 H), 3.63 (dd, $J = 9.2, 7.0$ Hz, 1 H), 4.00 (dd, $J = 2.2, 2.2$ Hz, 1 H), 4.54 (d, $J = 12.2$ Hz, 1 H), 4.56 (d, $J = 12.2$ Hz, 1 H), 4.64 (d, $J = 11.9$ Hz, 1 H), 4.70 (d, $J = 11.9$ Hz, 1 H), 5.47-5.54 (m, 1 H), 7.27-7.43 (m, 10 H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 20.56 (t'), 23.84 (t'), 36.35 (t'), 38.08 (d'), 41.99 (t'), 51.67 (d'), 71.18 (t'), 72.05 (t'), 73.31 (t'), 77.94 (d'), 120.26 (d'), 127.38 (d'), 127.66 (d'), 127.71 (d'), 128.43 (d'), 128.53 (d'), 138.09 (s'), 138.45 (s'), 147.10 (s'), 215.30 (s'); exact mass (HR electrospray) m/z calcd for $\text{C}_{25}\text{H}_{28}\text{NaO}_3$ ($M + \text{Na}$) 399.193615, found 399.193633.

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